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Editorial

Negative Pressure Breathing

THE physiological effects of negative pressure breathing, i.e., breathing against a pressure which is lower than ambient pressure, have received considerable attention in recent years. While data on this subject are still sparse, certain facts of interest have emerged. These have been derived from (1) direct studies of negative pressure breathing, (2) analysis of the negative phase of normal respiration, and (3) the effects of positive pressure breathing.

Negative Pressure Breathing and Lung Function. The pressure-volume relationships of the human thorax, according to Fenn [*1*] (Fig. 1), are such that alterations in lung volume occur in both the positive and negative phases of the respiratory cycle. With *positive* pressure breathing there is expulsion of blood from the thoracic cavity and an increase in the total lung capacity due to an increment in both residual volume and vital capacity. The vital capacity itself has two components: inspiratory capacity, which is decreased under these circumstances, and the expiratory reserve volume, which is increased under these circumstances.

The changes on the *negative* pressure side of the pressure-volume curve are directly opposite to those encountered with positive pressure. There is an increase in thoracic blood volume, a reduction in total lung capacity, residual volume and vital capacity, with an increase in inspiratory reserve and decrease in expiratory reserve volume. The reduction in vital capacity is in part due to the increase in blood in the thorax, but must also be attributed to the significant effort required during breathing from a negative pressure tank. In patients breathing from a negative pressure tank on inspiration only, at pressures varying from −10 to −16 cm. of water, the vital capacity is unchanged or only slightly decreased compared to control values at ambient pressures [*3*]. If the subjects are not breathing against markedly negative pressures, the changes observed are small. In the measurement of the maximum breathing capacity the difficulty accompanying breathing against a negative pressure is even more apparent. Subjects in our laboratory have uniformly shown a decrease of maximum breathing capacity against negative pressure [*3*].

Of particular interest in this connection is the tidal volume. In the pressure-volume curve of Fenn [*1*] (Fig. 1) there is an expansion of the tidal volume band on the *negative* side of the respiratory cycle. At zero pressure the relaxation-pressure curve of the lung touches the tidal volume band at the lower margin; during the negative phase of the respiratory cycle the relaxation-pressure curve falls below the tidal volume. This implies that in the negative pressure range, inspiratory pressure must be maintained to keep the lung from collapsing.

In considering these effects on lung volume we should not exclude the important factor of mid-position of the lung. It has been shown that the mid-position changes with *positive* pressure breathing [*4*], and it is possible, although this has not been established, that it may also be altered with *negative* pressure breathing. The data collected so far in our laboratory relating to vital capacity and maximum breathing capacity would seem to indicate that the changes encountered with breathing against intermittent

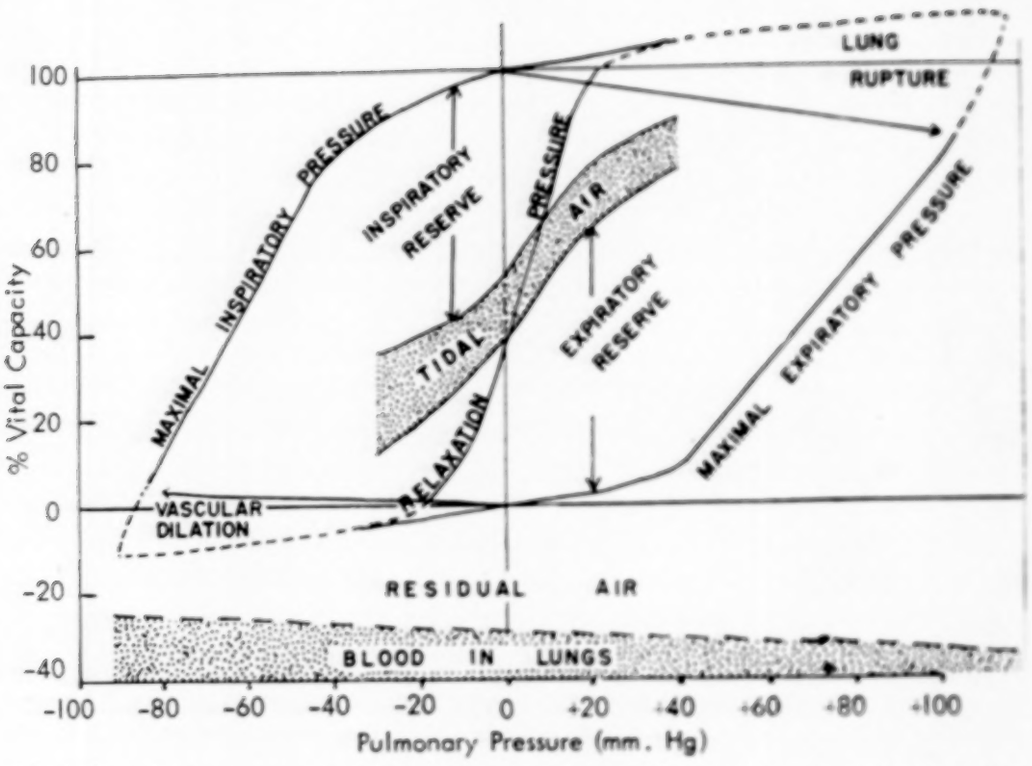

FIG. 1. Pressure-volume diagram of the human chest. (From: FENN, W. O. *Am. J. Med.* [1], after data of RAHN, H., OTIS, A. B., CHADWICK, L. E. and FENN, W. O. *Am. J. Physiol.* [2].)

negative pressure are compatible with those predicted from the pressure-volume curve of Fenn.

The effort required to breathe against negative pressure is considerable, although varying of course with the extent of negative pressure imposed upon the system. The accessory muscles of respiration must be called into play. Ventilation against negative pressure must therefore be accompanied by a significant increase in the work of breathing. It is of interest that there is also an increase in the work of breathing with continuous positive pressure breathing [5].

Cardiovascular Effects. Together with the altered mechanics of breathing, alterations in thoracic blood volume must be considered in studies of the effects of pressure breathing. It has been estimated that the amount of blood expelled from the chest during *positive* pressure breathing amounts to 200 to 500 cc. [6]. Similarly, it has been demonstrated that with the Valsalva maneuver blood is expelled from the thoracic viscera. With the Mueller maneuver, which effects a *negative* intrathoracic pressure, a comparable amount of blood is drawn into the thoracic cavity [7]. These changes in blood volume play a significant role in the alterations of lung volumes already discussed.

As a consequence of altered intrathoracic blood volume, changes in venous pressure take place. Although there is a reduction of blood in the intrathoracic vessels during *positive* pressure breathing, which would be expected to lead to a reduction in venous pressure, a net rise in venous pressure occurs because of the increase in intrathoracic pressure. Rahn et al. [8] have shown that this rise in venous pressure is equal to 50 per cent of the increase in intrathoracic pressure.

By analogy, with *negative* pressure breathing one would expect that with the larger volume of intrathoracic blood a rise in venous pressure would occur but here too the venous pressure is affected primarily by the decreased intrathoracic pressure, and actually falls. In our laboratory catheterization of the right heart in man has demonstrated that breathing against intermittent negative pressure results in a fall in right atrial pressure [3]. The lungs thus serve as a pool for the redistribution of blood. Indeed, postural changes alone, as demonstrated by Sjöstrand [9], result in alteration of the thoracic blood volume. Thus in going from the upright to the recumbent posture as much as 640 cc. of blood, or about 11 per cent of the blood volume, shifts from the lower extremities. Of

this volume, 78 per cent is picked up in the thorax, and of this, 75 per cent in the lungs. Despite the expected vascular pressure changes with positive and negative pressure breathing, it is apparent that the resultant intravascular pressure is primarily the result of the applied external breathing pressure affecting intrathoracic pressure and not a consequence of the redistribution of blood volume.

Within narrow ranges of pressure variations around zero pressure, little change in cardiac output occurs. However, with *positive* pressure breathing in the range of the pressures commonly employed in the use of positive pressure breathing apparatus, there is a demonstrable reduction of 15 to 25 per cent in cardiac output. Rahn et al. [8] noted that with a peak mask pressure of 22 cm. of water a reduction of 27 per cent of cardiac output takes place. Similarly, Cournand and co-workers [10] have shown that with positive pressure breathing there is a reduction in cardiac output primarily due to a reduction in venous return. Using the blue dye technic, Kilburn, Sieker and Murdaugh [11] have demonstrated a small reduction in cardiac index and stroke volume with positive pressure breathing. In contrast, with *negative* pressure breathing the cardiac index increases from 2.85 ± 0.18 to 3.98 ± 0.30 L./minute/M^2 while the stroke volume rises from 68.3 ± 4.3 to 95.4 ± 9.3 cc. [11]. This increase is small and has not been invoked to explain alterations in urine flow (to be described later) which occur with negative pressure breathing.

Changes in peripheral blood flow reflect those in cardiac output. With *positive* pressure breathing there is a reduction in blood flow to the limbs and to the digits [5], associated with vasoconstriction of the arterial tree peripherally. With *negative* pressure breathing [12] there is an increase in forearm blood flow. These changes are mediated via a nervous reflex [12]. No consistent changes in hand blood flow are seen.

Reduction in the cardiac output with *positive* pressure breathing, accompanied as it is by peripheral vasoconstriction, results in no significant change in systemic blood pressure. With *negative* pressure breathing there is likewise no significant alteration in systemic blood pressure.

Blood volume changes are of relevance in view of the remarkable effects of pressure breathing on urine flow. With positive pressure breathing it has been shown that the plasma volume is altered only slightly, usually in the direction of decrease [11,13]. There is no significant change in plasma volume during negative pressure breathing [11].

Effects on Renal Function and Water Metabolism. The area of greatest interest in connection with negative pressure breathing is concerned with renal function and the excretion of water. It is not the purpose of this editorial to discuss volume regulators within the circulation generally; this subject has been lucidly analysed by Smith [14].

Positive pressure breathing results in an antidiuresis [15], the reduction in urine flow reaching from 20 to 50 per cent of the normal output, depending on the level of pressure breathing. This antidiuresis may last from one to two hours after the test breathing period. Sieker, Gauer and Henry [16], who have contributed so much to the understanding and clarification of this field, demonstrated that with continuous *negative* pressure breathing there is a significant diuresis. This diuresis is not accompanied by any significant change in renal hemodynamics [16–18] and there is little or no change in electrolyte excretion [16–19]; indeed, significant natriuresis does not occur during negative pressure breathing even in individuals predisposed to sodium loss [19]. The diuretic effect of negative pressure is not related to nervous control of renal function [20].

It follows that the diuresis observed with negative pressure breathing is primarily due to increased free water clearance. There is no significant change in osmolar concentration of the plasma or in the peripheral venous hematocrit [18]. The diuresis is inhibited by the administration of antidiuretic hormone [17,18].

In an attempt to determine the mode of action by which negative pressure breathing produces diuresis Henry et al. [21] distended the pulmonary arterial tree by embolization with plastic beads, without significant effect on urine output. Similarly, snares placed on the pulmonary veins near the origin from the heart did not effect a significant alteration [21]. When these same workers employed a balloon expanded in the left atrium they were able to bring about a significant diuresis. From these data they concluded that there are left atrial receptors which influence urine flow. The possibility that these receptors lie in the ostia of the pulmonary vein was also considered. It had been shown by Whitteridge [22] that afferent nerve fibers run from the heart and lungs in the cervical vagus. Paintal [23] was, in fact, able (in cats) to isolate

fibers in the vagus leading from right and left atrial receptors, and Henry and Pearce [*24*] reported isolation in the dog of afferent fibers running in the vagus, with discharge characteristics of the cardiac atrial stretch fibers previously demonstrated in the cat. These fibers are stimulated by stretch and not by pressure. Thus maximum nerve impulse was not picked up during atrial systole when the pressure is maximal but at the end of diastole when the volume was maximal. These, then, are stretch receptors, not baroreceptors. Cooling of these fibers blocked conduction. The fibers were stimulated by inflation of a left atrial balloon, or by negative pressure breathing, or by sudden increase in the blood volume by infusion of saline solution; conversely, less stimulation of these afferent fibers occurred when hemorrhage took place [*24*].

It would appear, then, that negative pressure breathing produces a diuresis via a neurohormonal mechanism. This is initiated by stretch receptors located in the left atrium or at the ostia of the pulmonary veins, with impulses via afferent fibers in the vagus, leading through some undefined path to inhibition of the secretion of antidiuretic hormone.

Many gaps remain in our knowledge of the alterations in physiological activities under the influence of negative pressure breathing. Since newer respiratory apparatus are being constructed in which a negative pressure phase is incorporated, it becomes increasingly important from a practical standpoint to learn more about the cardiorespiratory and other effects of negative pressure breathing. Perhaps from such studies additional information, as significant as the discovery of the left atrial stretch receptors may be garnered.

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Clinical Studies

Hemodynamic Patterns in Chronic Cardiac Failure*

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With the advent of cardiac catheterization it became possible to undertake a direct study of the dynamic events associated with failure of the heart in man. Pioneer studies in the laboratories of Cournand, McMichael, Stead and others permitted clarification of the concept of heart failure, a subject of considerable controversy. Thus it was possible to demonstrate that the two ventricles may fail independently of each other, and that an abnormally low cardiac output is not necessarily an essential feature of congestive cardiac failure. The state of compensation on the one hand, and of failure of the heart on the other, had to be re-defined in a more comprehensive manner in terms of a wide spectrum of hemodynamic disturbances involving not only abnormalities of flows or pressures *per se*, but also their relation to the metabolic demands of the organism and their response to stress and exercise.

Most investigators studied the dynamics of cardiac failure during its symptomatic stage, in which failure of the left side of the heart, of the right side of the heart, or of both ventricles was clinically evident. Studies of the effect of cardiotonic drugs demonstrated the reversibility of some aspects of cardiac failure, for it was shown that effective treatment may partially or completely correct the characteristic hemodynamic abnormalities.

The purpose of this study was to investigate an aspect of cardiac failure which has hitherto received only scant attention: the persistence of hemodynamic abnormalities in patients with chronic cardiac disease affecting primarily the left ventricle, who were previously in failure and were brought under control by medical treatment.

MATERIAL AND METHODS

The series consists of fifty patients, all of whom had entered the hospital with evidences of cardiac failure. Forty-nine were males, one female. Only those patients were included in the study in whom the cardiac lesion was shown to affect the left ventricle primarily. Thus patients with mitral valve disease, pulmonary heart disease and congenital cardiac disease were excluded. Furthermore, patients in cardiac failure in whom the findings suggested the presence of hypermetabolic or high output states were also excluded from the study in an effort to deal with a physiologically homogenous group of subjects with chronic left ventricular overload with "low output failure."

A clinical history was obtained and a physical examination performed upon admission to the hospital. The clinical diagnosis of "arteriosclerotic" heart disease, an admittedly unsatisfactory but universally accepted term, was used in patients with evidence of chronic damage to the myocardium caused by coronary artery disease, which led to cardiac failure. Patients in whom cardiac failure developed following a major myocardial infarction were separated from the former group. Hypertensive cardiovascular disease comprised the second largest group of cases. The diagnosis was established in the presence of persistent diastolic hypertension, present or past, with evidence of left ventricular hypertrophy and dilatation in the electrocardiogram and the roentgenogram. In cases in which hypertension and coronary artery disease coexisted, the diagnosis was listed according to the factor which appeared to dominate the clinical picture. The third group of cases included cardiac failure due to aortic valvular disease. In young patients with a history of rheumatic disease, a rheumatic etiology was accepted; older patients with calcific aortic stenosis are indicated without etiological diagnosis. Three patients with idiopathic myocarditis, proved at necropsy, also have been included.

All patients were given the conventional therapeutic regimen immediately after admission to the

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TABLE 1

SUMMARY OF CLINICAL DATA OF FIFTY PATIENTS, ARRANGED IN HEMODYNAMIC GROUPS AT THE TIME OF HOSPITAL ENTRY

Case No.	Patient's Initials	Age (yr.)	Diagnosis*	Duration of Failure	LVF†	RVF‡	ECG§	X-ray¶	Progress
				Group 1					
1	J. B.	65	ASHD	8 mo.	+	–	AR	+ + +	Good
2	J. B.	64	HHD	2 mo.	+	+	LVH	+ +	Good
3	W. D.	62	ASHD	10 days	+ + +	+ + +	LBBB	+ +	Good
4	W. O.	67	HHD	4 mo.	+ +	+ +	BR	–	Good
5	C. S.	36	HHD	10 mo.	+	–	LVH	+ +	Good
6	L. P.	61	HHD	1 yr.	+	–	BR	+	Good
7	S. M.	51	ASHD	Few mo.	+	–	LVH	+ +	Fair
8	W. L.	65	Old MI	2 yr.	+	+	Old MI	+ +	Good
9	H. S.	33	HHD	2 yr.	+	–	LVH	+	Good
				Group 2					
10	W. C.	68	Calcific AS	2 wk.	+ +	+ +	LVH	+ +	Fair
11	G. H.	73	ASHD, AF	Few mo.	+	+	LVH		Poor
12	G. H.	75	HHD, AF	Few mo.	+ +	+	LVH	+ +	Good
13	J. K.	77	HHD	4 mo.	+ +	+	LVH	+	Good
14	H. S.	54	ASHD	1 mo.	+ + +	+ + +	AR	+ + +	Fair
15	W. S.	69	HHD, AF	3 wk.	+ +	+ +	AR	+ +	Fair
16	E. L.	58	HHD	1 yr.	+	+	AR	+ +	Good
17	I. W.	76	ASHD, AF	3 mo.	+	–	RBBB	+ +	Good
18	M. M.	71	ASHD	2 wk.	+ + +	+ +	AR	+ +	Good
19	J. E.	69	HHD	9 mo.	+	–	NR	+	Good
20	W. C.	67	ASHD, AF	2 yr.	+	–	AR	+ +	Good
21	J. G.	33	Myocarditis	2 wk.	+ +	–	AR	+ + +	Good
22	E. K.	35	HHD, AF	10 days	+	–	LVH	+ +	Good
				Group 3A					
23	E. E.	62	ASHD	10 days	+ +	+ +	LVH	+ +	Fair
24	I. G.	46	RHD, AS	1½ yr.	+ +	+	AR	+	Good
25	B. G.	72	ASHD	1 yr.	+ +	+	LVH	+ +	Poor
26	S. P.	58	HHD, AF	3 wk.	+ +	–	LVH	+ +	Fair
27	R. B.	59	Symphilitic AI	1½ mo.	+ +	–	LVH	+ +	Good
				Group 3B					
28	J. B.	62	ASHD	2 wk.	+	–	AR	+ +	Fair
29	B. B.	62	Old MI	2 yr.	–	+ +	LVH, MI	+ + +	Fair
30	J. C.	63	Old MI	3 wk.	+ +	+ +	LVH	+ +	Good
31	A. C.	69	ASHD	6 mo.	+ + +	+ +	LVH	+ + +	Good
32	R. H.	43	Myocarditis	3 mo.	+ +	–	LBBB	+ +	Poor
33	R. H.	47	ASHD	2 yr.	+ + +	+ +	AR	+ +	Fair
34	G. K.	43	Myocarditis	10 mo.	+ +	–	LBBB	+ + +	Poor
35	V. M.	59	ASHD	1 yr.	+ +	+	AR	+ +	Poor
36	E. T.	49	Old MI, AF	2 yr.	+ +	+ +	LVH, MI	+ +	Poor
37	R. W.	35	HHD	2 yr.	+ +	+	LVH	+ +	Good
38	F. C.	46	Old MI	2 mo.	+	–	MI	+ +	Poor
39	C. K.	75	Calcific AS	6 yr.	+ +	–	LVH	–	Fair
40	L. K.	60	RHD, AI	1 yr.	+	–	LVH	+ + +	Good
41	J. B.	65	Calcific AS	2 yr.	+ +	+	LVH	+ +	Fair

TABLE 1 (*Continued*)

SUMMARY OF CLINICAL DATA OF FIFTY PATIENTS, ARRANGED IN HEMODYNAMIC GROUPS AT THE TIME OF HOSPITAL ENTRY

Case No.	Patient's Initials	Age (yr.)	Diagnosis*	Duration of Failure	LVF†	RVF‡	ECG§	X-ray¶	Progress
				Group IC					
42	P. C.	49	HHD	3 yr.	++	++	RBBB	+	Good
43	J. D.	44	ASHD, AF	3 wk.	+++	+++	AR	++	Good
44	M. G.	72	ASHD, AF	3 mo.	++	++	AR	++	Fair
45	A. H.	50	HHD	4 wk.	++	++	LVH	+++	Good
46	F. L.	63	HHD	1 yr.	+	+	LVH	++	Good
47	F. N.	57	HHD	3 days	++	+	LVH	+	Good
48	I. N.	55	Old MI	8 mo.	++	++	LVH, MI	+	Fair
49	J. S.	56	Old MI	8 mo.	+++	++	LBBB	+++	Fair
50	E. E.	53	RHD, AS	3 yr.	+++	+++	RVH	++	Fair

* ASHD = arteriosclerotic heart disease; HHD = hypertensive heart disease; MI = myocardial infarction; AS = aortic stenosis; AF = atrial fibrillation; AI = aortic insufficiency.

† LVF = left ventricular failure, graded + mild; ++ moderately severe; +++ severe.

‡ RVF = right ventricular failure, graded same as LVF.

§ ECG = electrocardiogram; AR = abnormal, non-diagnostic record; LVH = pattern of left ventricular hypertrophy; RVH = right ventricular hypertrophy; BR = borderline record; NR = normal record; BBB bundle-branch block.

¶ X-ray = degree of cardiac enlargement, graded as none (−), mild (+), moderate (++) and severe (+++).

hospital. This consisted of rest, sodium restriction, the administration of digitalis and diuretics. Cardiac catheterization studies were performed when the patient was considered to have reached a plateau of clinical response to cardiac therapy. The achievement of a "chronic state" of cardiac failure was recognized by the following criteria: (1) attainment of a "dry weight"; (2) disappearance or stabilization of clinical symptoms and signs of cardiac failure; and (3) presence of a ventricular rate under 80 beats per minute at rest, in patients with atrial fibrillation. At the time of cardiac catheterization four-fifths of the patients showed no clinical evidence of cardiac failure; one-fifth could be considered in a state of chronic, stabilized cardiac failure. Almost all the patients were able to perform, without undue discomfort, the mild standardized exercise test during the catheterization study.

Hemodynamic measurements were performed during the catheterization study, the methodology of which has been described in detail elsewhere [*1,2*]. All patients were prepared by a sham study the afternoon before the test, during which they were acquainted with the technic of air collection and exercise. The actual study was carried out with the patient in postabsorptive state without sedation. Two determinations of cardiac output were made at rest, after which the patients underwent the standard exercise test during which they slowly moved pedals, with a resistance attached to them, back and forth in the recumbent position. This exercise test was shown to increase consistently the oxygen consumption between 75 and 125 per cent above the basal level. Exercise was performed for a period of not less than five minutes, air and blood collections being made during the final two minutes of this period. Intracardiac and arterial pressures were recorded by means of Statham strain gauges (P 23D) attached to the Sanborn multichannel oscillographic direct writing recorder. Pressures were referred to a zero point halfway between the sternum and the spinous process of the recumbent patient. This zero level was rechecked at frequent intervals. Mean pressures were obtained by electrical integration. Pulmonary wedge pressures were recorded at the beginning of the study and were accepted only if they fulfilled all the criteria for validity [*1*]. Following the recording of pulmonary wedge pressures, the catheter tip was withdrawn under fluoroscopic control into the main pulmonary artery, in which it stayed for most of the remainder of the study, and from which a continuous recording of pressure was obtained, using slow paper speed (½ mm. per second). Right ventricular and right atrial pressures were recorded at the time of final withdrawal of the catheter.

RESULTS

A clinical summary of the fifty cases included in this study is presented in Table 1. As indicated, sixteen patients were classified as having arteriosclerotic heart disease; seventeen

patients as having hypertensive heart disease; in seven failure developed following myocardial infarction; seven patients had aortic valvular heart disease and three had idiopathic myocarditis. Sinus rhythm was present in forty patients at the time of the study, ten had chronic atrial fibrillation. There was a wide variation in findings and in symptomatology, from acutely developing cardiac failure immediately before hospital admission, to longstanding disability due to chronic symptomatology. The last column in Table I indicates the response to therapy while in the hospital: the notation "good" refers to patients in whom cardiac therapy brought signs and symptoms of failure under prompt and satisfactory control; "moderate" refers to patients in whom only partial elimination of failure was obtained, and "poor" to those who remained in cardiac failure in spite of vigorous therapy.

The hemodynamic data revealed a wide variety of abnormalities. It became evident that, rather than degrees of hemodynamic abnormalities, important differences occur in cardiac failure which suggest qualitatively different patterns. The material was accordingly divided into groups of hemodynamically similar cases.

The circulatory findings fell into two general categories: (1) Cases in which the resting level of pulmonary wedge pressure was normal, indicative of a normal left ventricular end-diastolic and left atrial pressure, suggesting recovery from left ventricular failure which presumably existed at the height of clinical evidence of cardiac failure. (2) Cases in which there was a persistent elevation of resting left atrial pressure which could then be termed "chronic left ventricular failure."

Table II includes all patients with normal or borderline resting left atrial pressure, as evidenced by pulmonary wedge pressure readings of 15 mm. Hg or less (groups 1 and 2). These patients, twenty-two in all, have been arbitrarily divided into group 1, showing a normal or near normal cardiac output (evidenced by an arteriovenous oxygen difference of less than 5.5 vol. %), and group 2 with an abnormally low cardiac output. In group 1, all patients had a normal right atrial pressure and normal pulmonary vascular resistance. Resting pulmonary arterial pressures were normal or equivocally elevated. The response to exercise was definitely abnormal in all but one case (W. O.), since there was a rise in pulmonary arterial pressures, and the abnormal widening of the arteriovenous oxygen difference (over 2 vol. %) indicated an inadequate increase in cardiac output in relation to oxygen demands [*1*]. The thirteen patients in group 2 showed abnormally low resting cardiac outputs. In these instances pulmonary arterial pressures were often higher at rest than in group 1, and many patients showed a steeper rise with exercise. Abnormally high pulmonary vascular resistance was occasionally encountered, in five patients reaching a level over 300 dynes/second/cm^{-5}, or more than twice the average normal value. The right atrial pressures were normal in all patients. The cardiac output often reached very low levels, less than 1.75 L./minute/m^2 in four patients. The rise in cardiac output during exercise was inadequate in eleven of thirteen patients.

Table III presents the patients in group 3, chronic left ventricular failure, who were subdivided into three categories: The first subdivision, A, includes five patients with sustained elevation of left atrial pressure associated with a normal or near-normal cardiac output. In these cases pulmonary artery wedge pressure ranged from 17 to 23 mm. Hg and pulmonary arterial mean pressures from 27 to 42 mm. Hg, thus indicating mild, passive pulmonary hypertension. Pulmonary vascular resistance was normal or slightly elevated.

Subdivisions B and C of this group exhibited subnormal values of cardiac output. Subdivision B includes such patients with a normal, mildly or moderately elevated pulmonary vascular resistance. Subdivision C includes the "high resistance" group of patients in whom the pulmonary vascular resistance exceeded 600 dynes/second/cm^{-5}. In subdivision B, the cardiac output was slightly lower, on the average, than in the corresponding group 2 and showed even less increase with exercise than in the latter. Pulmonary wedge pressure measurements indicated levels between 16 and 36 mm., and pulmonary arterial pressures showed more severe degrees of pulmonary hypertension than in group 1, the mean pulmonary vascular resistance being twice as great in B as in A. Half of the patients in this subdivision showed right atrial pressures over 10 mm. Hg, indicating some degree of right as well as left ventricular failure.

Subdivision 3C included nine patients who can be classified as having severe pulmonary hypertension, with pulmonary vascular resist-

TABLE II

SUMMARY OF HEMODYNAMIC FINDINGS IN PATIENTS WITH NORMAL AND BORDERLINE ELEVATION OF LEFT ATRIAL PRESSURE

Patient's Initials	O_2 Consumption (cc./min.)		O_2 A-V Difference (vol. %)		Cardiac Index (L./min./m²)		Pulmonary Wedge Pressure (mm. Hg)		Pulmonary Arterial Pressure (mm. Hg)		Mean Pulmonary Arterial Pressure (mm. Hg)		Right Atrial Pressure (mm. Hg)		Pulmonary Vascular Resistance (dynes/sec./cm⁻⁵)	
	R	E	R	E	R	E	R	E	R	E	R	E	R	E	R	E
Group 1																
J. B.	225	....	3.9	....	3.15	....	10	..	30/12	.....	15	..	6	..	90	..
J. B.	276	625	5.1	7.4	2.52	3.96	10	..	27/10	39/15	15	27	7	..	96	..
W. D.	250	558	5.0	9.5	2.92	3.47	8	..	28/12	48/12	18	30	3	..	160	..
W. O.	350	545	4.2	5.8	4.10	5.31	15	..	38/16	45/19	21	25	6	..	90	..
C. S.	260	609	5.1	8.3	2.91	4.28	10	17	30/15	66/33	21	45	1	..	171	..
H. S.	314	670	4.6	8.4	3.66	4.02	14	..	34/15	38/20	23	30	7	..	105	..
L. P.	238	386	5.4	6.4	2.35	3.21	12	..	25/15	47/17	19	28	4	..	128	..
S. M.	215	622	5.1	9.7	2.50	3.10	9	..	32/15	60/33	20	45	6	..	188	..
W. L.	191	412	5.2	8.2	2.49	3.41	12	..	23/15	35/17	18	25	3	..	66	..
Mean value	257	541	4.8	7.9	2.95	3.84	11	..	29/14	47/22	19	31	5	..	122	..
Group 2																
W. C.	238	600	6.2	9.9	1.95	3.05	15	..	34/15	71/30	21	42	6	..	124	..
G. H.	221	332	7.5	11.9	1.67	1.52	10	..	33/13	65/20	18	35	3	..	200	..
G. H.	215	362	6.8	7.7	1.82	2.60	8	..	31/12	43/17	18	28	..	..	251	..
J. K.	232	355	7.1	9.7	2.02	2.26	14	..	32/15	36/14	20	20	7	..	165	..
H. S.	249	472	7.8	10.9	1.74	2.34	9	..	31/13	49/28	22	45	7	..	320	..
W. S.	235	517	7.5	9.9	1.69	2.81	12	..	29/14	51/18	19	32	4	..	176	..
E. L.	212	412	5.6	6.8	2.30	3.60	10	..	31/12	47/20	20	32	6	..	217	..
I. W.	261	508	8.6	13.2	1.61	2.16	8	..	26/13	30/15	18	21	4	..	272	..
M. M.	240	574	5.7	9.3	2.44	3.14	8	..	35/12	40/14	24	27	7	..	304	..
J. E.	214	525	6.3	9.5	1.95	3.18	7	..	25/13	29/14	14	16	5	..	164	..
W. C.	243	540	6.5	11.0	1.97	2.59	8	..	45/21	65/31	25	40	6	..	362	..
J. G.	230	482	6.5	10.5	1.86	2.40	11	..	39/16	75/30	30	48	8	..	425	..
E. K.	281	523	6.0	8.8	2.34	2.77	7	..	27/9	34/18	13	18	4	..	103	..
Mean value	235	477	6.7	9.9	1.82	2.67	10	..	33/14	52/22	21	33	6	..	243	..

NOTE: R = resting value; E = during exercise.

ance more than four times the normal value. In this group the cardiac output was noted to be very low, and even more apt to remain unchanged during exercise than in the other groups. Pulmonary wedge pressures were high but not, as a rule, higher than in subdivision 3B. Pulmonary arterial pressures revealed markedly hypertensive levels, with further increase during exercise, which may occur even in the absence of an increase in cardiac output. The majority of patients had an elevation of right atrial pressure, some of which was associated with tricuspid valve regurgitation.

As indicated in Tables II and III, the cardiac output appears to be lowered in patients with increased pulmonary vascular resistance. This relationship was further explored by plotting the cardiac output against pulmonary vascular resistance. (Fig. 1.) The scatter graph demonstrates that normal cardiac output is found only in the presence of normal pulmonary vascular resistance, and that when pulmonary vascular

TABLE III

SUMMARY OF HEMODYNAMIC FINDINGS IN PATIENTS WITH ELEVATED LEFT ATRIAL PRESSURE

Patient's Initials	O_2 Consumption (cc./min.)		O_2 A-V Difference (vol. %)		Cardiac Index (L./min./m²)		Pulmonary Wedge Pressure (mm. Hg)		Pulmonary Arterial Pressure (mm. Hg)		Mean Pulmonary Arterial Pressure (mm. Hg)		Right Atrial Pressure (mm. Hg)		Pulmonary Vascular Resistance (dynes/sec./cm⁻⁵)	
	R	E	R	E	R	E	R	E	R	E	R	E	R	E	R	E
Group 3A																
E. E.	290	514	4.7	7.7	3.06	3.23	24	..	69/29	92/39	39	60	6	..	196	..
I. G.	283	542	5.0	8.7	3.18	3.65	23	..	69/15	82/25	42	53	12	..	268	..
B. G.	191	480	4.3	7.9	2.27	3.10	21	..	60/22	90/40	36	57	6	..	250	..
S. P.	265	692	4.4	8.0	3.24	4.30	17	..	40/18	54/25	27	36	4	..	139	..
R. B.	315	625	5.5	9.9	3.41	3.84	21	..	45/22	69/32	30	52	8	..	135	..
Mean value	268	570	4.8	8.5	3.01	3.63	21	..	54/23	77/36	35	52	7	..	199	..
Group 3B																
J. B.	188	...	6.8	...	1.68	....	25	..	75/39	.....	43	..	12	..	580	..
B. B.	320	...	8.9	....	2.1	....	35	..	85/36	.....	60	..	18	..	480	..
J. C.	210	...	6.4	....	1.8	....	25	..	56/27	.....	38	..	6	..	310	..
A. C.	236	414	9.8	12.1	1.42	1.75	16	..	39/15	45/22	27	33	6	..	329	..
R. H.	227	260	8.0	9.0	1.70	1.75	24	..	32/20	40/21	30	33	11	..	171	..
R. H.	208	405	5.7	9.0	2.07	2.56	30	..	53/30	57/39	35	43	12	..	125	..
G. K.	251	505	6.5	10.8	2.02	2.48	22	..	38/24	52/38	29	42	8	..	230	..
V. M.	191	318	8.1	12.6	1.44	1.53	29	..	75/28	89/41	42	60	13	..	442	..
E. T.	265	374	6.3	8.3	2.06	2.15	20	..	40/20	56/28	36	39	18	..	189	..
R. W.	288	473	7.0	10.2	2.31	2.61	36	..	80/40	85/45	45	50	9	..	410	..
F. C.	313	491	10.3	12.5	1.59	2.06	38	..	70/30	83/39	54	66	15	..	425	..
C. K.	226	483	6.6	10.1	2.11	2.92	15	..	40/17	86/33	30	60	7	..	350	..
L. K.	195	379	8.2	12.5	1.50	1.91	30	..	61/21	78/41	41	60	4	..	425	..
J. B.	265	482	9.3	15.4	1.64	1.82	16	..	52/23	70/32	30	42	2	..	510	..
Mean value	240	423	7.7	11.0	1.76	2.11	26	..	57/27	69/34	39	48	10	..	354	..
Group 3C																
P. C.	308	429	7.7	9.6	2.16	2.41	18	..	82/24	110/32	53	72	5	..	690	..
J. D.	243	432	7.0	14.1	1.87	1.65	30	..	70/48	80/52	57	63	20	..	640	..
M. G.	197	466	5.6	12.8	2.12	2.23	22	..	81/36	97/49	50	75	15	..	800	..
A. H.	201	494	8.0	13.0	1.65	2.45	30	..	81/40	110/45	57	75	6	..	850	..
F. L.	290	435	8.6	12.0	1.16	1.25	35	..	80/46	88/51	63	66	16	..	680	..
F. N.	199	...	8.0	....	1.53	....	35	..	96/46	.....	65	..	8	..	920	..
I. N.	196	355	8.5	14.2	1.49	1.39	30	..	72/40	75/45	50	57	24	..	600	..
J. S.	247	400	7.8	11.7	1.95	2.11	24	..	65/27	79/35	45	55	10	..	610	..
E. E.	230	446	6.7	12.3	1.80	1.88	30	..	93/54	112/80	74	90	..	..	1020	..
Mean value	235	424	7.6	12.6	1.74	1.90	28	..	80/45	89/49	57	69	13	..	755	..

NOTE: R = resting value; E = during exercise.

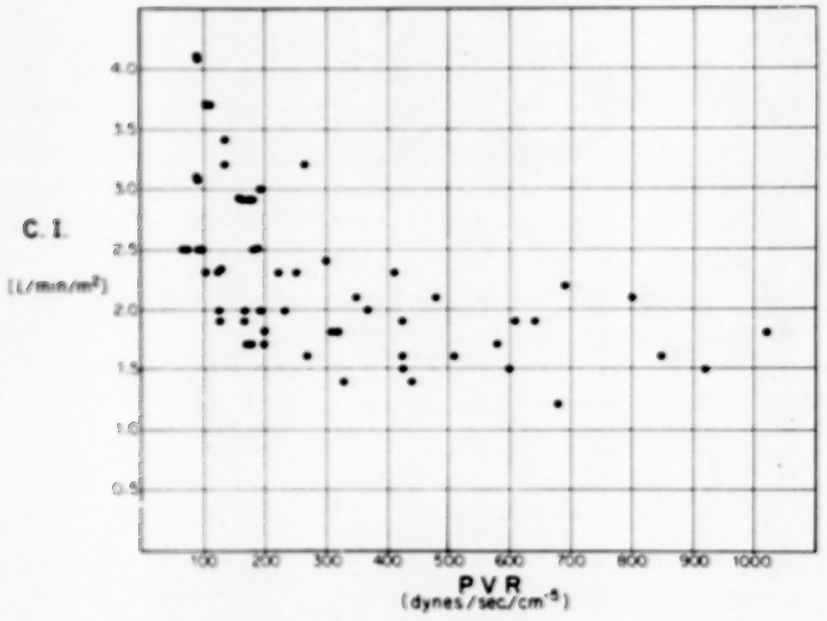

FIG. 1. Relationship between the cardiac output (C. I.) and the pulmonary vascular resistance (P. V. R.) in the series of fifty cases.

resistance exceeds 300 dynes/second/cm^{-5} the cardiac output invariably was less than 2.5 L./minute/m^2.

COMMENTS

The group of patients presented here can be considered physiologically homogeneous despite the unrelated etiological and anatomical factors represented. In all cases, chronic overloading of the left ventricle had led to failure. From the hemodynamic point of view, it seems irrelevant whether the increased left ventricular work was caused by increased resistance (hypertension or aortic stenosis), by an insufficient number of myocardial fibers to carry a normal load (fibrosis or infarction), or by increased stroke volume (aortic regurgitation). Once the overloaded left ventricle fails, a well known chain of events is initiated, including reduction of cardiac output, elevation of left atrial pressure, passive pulmonary venous and arterial hypertension and the resulting overload of the right ventricle, which may or may not lead to right ventricular failure.

This study is concerned not with the acute stage of left ventricular failure but with the chronic stage of recovery following its treatment. Before discussing the results of the observations reported here, it is necessary to review briefly earlier observations concerning recovery from cardiac failure. The observations on recovery from "low output failure" deal almost exclusively with acute studies on the circulatory effect of digitalis. It has been demonstrated that the administration of digitalis increases the abnormally low cardiac output in the majority of cases [*3–9*], although not completely to normal values in most cases. Studies of intracardiac pressures showed recovery from right ventricular failure, i.e., restoration of normal right atrial and right ventricular end-diastolic pressures. Pulmonary arterial pressures and right ventricular systolic pressures revealed significant decreases in response to digitalis administration, with restoration of normal levels in some instances and partial improvement in others. The pulmonary arterial hypertension found consistently in cardiac failure was, in the absence of left atrial pressure measurement, assumed to be caused by pulmonary venous and left atrial hypertension, and the response to digitalis administration was considered by the investigators to be indirect evidence of fall in left atrial pressure. Recovery from failure was studied by means of serial cardiac catheterization by Eichna et al. [*10*] in a small series of patients, with results indicating normalization of pressures and flows to be partial more often than complete in patients who made a clinical recovery from cardiac failure. The effect of exercise on patients with cardiac failure was studied by Hickam and Cargill [*11*], Ferrer et al. [*12*] and Lewis et al. [*13*], the last mentioned investiga-

TABLE IV

SUMMARY OF HEMODYNAMIC FINDINGS IN TWO PATIENTS IN WHOM SERIAL CATHETERIZATIONS WERE PERFORMED

Year	O_2 Consumption (cc./min.)		O_2 A-V Difference (vol. %)		Cardiac Index (L./min./m²)		Pulmonary Wedge Pressure (mm./Hg)		Pulmonary Arterial Pressure (mm./Hg)		Mean Pulmonary Arterial Pressure (mm./Hg)		Pulmonary Vascular Resistance (dynes/sec./cm⁻⁵)
	R	E	R	E	R	E	R	E	R	E	R	E	R
Patient A. H.													
1955	201	494	8.0	13.0	1.65	2.45	30	..	81/40	110/45	57	75	850
1957	237	476	9.0	13.4	1.65	2.25	34	..	78/41	95/50	60	65	795
Patient C. S.													
1955	230	395	5.5	8.8	2.4	2.5	12	..	36/12	46/21	20	33	150
1957	260	609	5.1	8.6	2.9	4.3	10	..	30/15	66/33	21	45	171

NOTE: R = resting value; E = during exercise.

tors including observations on left atrial pressure recorded through pulmonary arterial wedging. All these investigators showed accentuation of abnormal dynamics by exercise, as evidenced by inadequate increase in cardiac output in relation to oxygen consumption and rises in intracardiac pressures.

An analysis of the foregoing studies justifies three general conclusions: (1) clinically overt cardiac failure is associated with characteristic hemodynamic abnormalities showing a wide gradation in severity; (2) exercise accentuates the abnormalities, or brings them into being in latent cases; (3) clinical recovery from failure is more often associated with partial than with complete normalization of hemodynamics.

The observations reported in this study were made in patients recovering from cardiac failure at a time when they reached a clinically stable state. It has been assumed that they had also reached a stable hemodynamic state, that is, the circulatory dynamics had reached a plateau in the process of recovery from cardiac failure and no further improvement was likely. This assumption was based on the parallel course of clinical and hemodynamic recovery from failure noted by several investigators, and was strongly supported by the reproducibility of hemodynamic findings in two patients who underwent serial studies in the course of chronic cardiac failure at two-year intervals. (Table IV.)

The hemodynamic abnormalities found in the cases included in this study varied widely, yet did not represent a homogeneous continuum but fell into qualitatively different patterns. While the division into the groups representing these patterns has been made arbitrarily, the differences nevertheless were distinctive enough to suggest that there may be more than one mode of adaptation of the circulatory apparatus to left ventricular failure and to recovery therefrom.

Group 1 included all patients in whom the resting circulatory dynamics were within the range of normal. All but one patient can be termed as having "latent" left ventricular failure, because of abnormal response to exercise. The one patient who showed normal values at exercise as well was the only instance in the entire series of complete hemodynamic recovery from left ventricular failure. This emphasizes the rare occurrence of total return of the circulatory apparatus to normal, once cardiac failure is clinically evident.

Group 2 included patients in whom the resting left atrial pressure was within the normal range, but the cardiac output was abnormally low at rest. In this group pulmonary arterial pressures were normal or slightly elevated, and pulmonary

vascular resistance was normal in the majority of instances. All abnormalities were sharply accentuated by exercise.

Group 3 included all patients with elevation of left atrial pressure at rest, physiologically representing "chronic left ventricular failure." This group was divided arbitrarily into three subdivisions, which are thought to represent stages and sequelae of chronic left ventricular failure: (1) patients with the mildest cases in whom the resting cardiac output was within normal range, (2) patients with abnormally low resting cardiac output and pulmonary vascular resistance under *600* dynes/second/cm^{-5}, and (3) patients with marked elevation of pulmonary vascular resistance, unequivocal pulmonary hypertension.

The results of this study thus suggest that failure of the left ventricle due to chronic overload may respond to treatment in three ways, as is shown diagrammatically in Figure 2: (1) the circulatory dynamics may become normal at rest, in which case the response to exercise is still almost always abnormal; (2) left atrial (and ventricular end-diastolic) pressures may return to normal at the expense of abnormally low resting cardiac output; (3) the resting cardiac output may return to normal at the expense of abnormally high left ventricular filling pressure, as shown by the elevated left atrial pressure (chronic left ventricular failure). This last response is analogous to mitral stenosis and may set up a similar chain of events, in that pulmonary vascular resistance often rises, leading to right ventricular overload and possible failure. Increased pulmonary vascular resistance and tricuspid regurgitation, which frequently accompanies right ventricular failure [*11*], then tend to reduce the resting cardiac output, leading to the formation of groups 3B and 3C which represent patients with more advanced stages of pure left ventricular failure (group 3A).

Certain clinical implications are evident from the results of this study. It is evident, for instance, that patients with the most severe degree and longest duration of cardiac failure are not necessarily those with the most advanced residual chronic hemodynamic changes. In fact, there appears to be no relationship between the nature and severity of the hemodynamic abnormalities on the one hand, and the etiology, length of symptomatology and severity of cardiac failure on the other. It is also noteworthy that many patients with apparently satisfactory

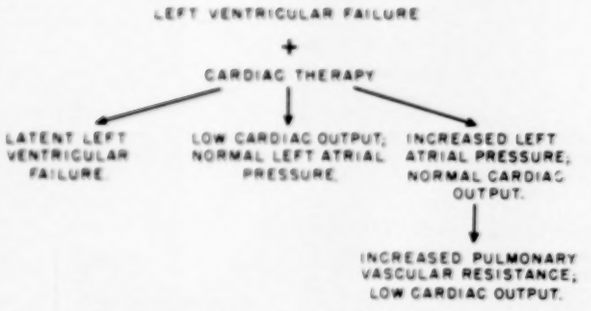
LEFT VENTRICULAR FAILURE
+
CARDIAC THERAPY
LATENT LEFT VENTRICULAR FAILURE
LOW CARDIAC OUTPUT; NORMAL LEFT ATRIAL PRESSURE
INCREASED LEFT ATRIAL PRESSURE; NORMAL CARDIAC OUTPUT
INCREASED PULMONARY VASCULAR RESISTANCE; LOW CARDIAC OUTPUT

FIG. 2. Hemodynamic responses to therapy in cardiac failure.

clinical recovery from cardiac failure, and showing relatively little disability, nevertheless have chronic hemodynamic abnormalities of advanced degree.

The observations reported in this study demonstrate one aspect of the pathophysiology of cardiac failure which is not sufficiently appreciated, namely that a patient with cardiac disease may be physiologically in chronic left ventricular failure, as evidenced by a left atrial pressure of 25 mm. Hg or higher, and yet be almost free of cardiac symptoms. This is not at all surprising when one considers the common occurrence of similarly high left atrial pressures in virtually asymptomatic patients with mitral stenosis. However, in contrast to mitral stenosis in which a stable state is inherent in mechanical obstruction of the mitral orifice, the asymptomatic state in left ventricular failure depends on provision by medical management of support for the weakened myocardium, and symptoms are likely to recur if the proper therapeutic regimen is discontinued.

Hemodynamically evident left ventricular failure antedating the clinical manifestations of failure was not encountered in the present study because patients were investigated only following recovery from cardiac failure. Other investigators, who studied the circulatory dynamics of patients with cardiac disease who were never in failure [*7,15,16*] found normal hemodynamics as a rule. This may be interpreted as suggesting that the onset of cardiac failure is usually not a gradual process with a latent period preceding the clinical manifestations thereof but rather that failure may occur acutely, with parallel clinical and physiological manifestations.

SUMMARY AND CONCLUSIONS

A study was made of a group of fifty patients with chronic left-sided cardiac lesions (hyper-

tensive, arteriosclerotic cardiac disease, aortic valve lesions and myocarditis) who entered the hospital in overt cardiac failure. All the patients were given conventional treatment for cardiac failure, and observed clinically until "dry" weight was attained and they were rendered asymptomatic at rest. Four-fifths of the patients then showed no clinical evidence of cardiac failure and many were able to resume normal activities.

At this point cardiac catheterization studies were performed for the purpose of assessing chronic residual hemodynamic changes in patients who recovered from cardiac failure. Only one patient showed entirely normal circulatory dynamics. Forty-nine patients fell into one or another of the following hemodynamic groups: (1) normal resting dynamics with abnormal response to exercise; (2) normal resting left atrial pressure with an abnormally low resting cardiac output; (3) elevated left atrial pressure with a normal resting cardiac output; (4) elevated left atrial pressure with increase in pulmonary vascular resistance and low cardiac output. Nine patients in the last category were found to have marked pulmonary hypertension with a pulmonary vascular resistance more than 600 dynes/second/cm^{-5}.

The findings of this study are interpreted as showing qualitative differences in the adaptation of the circulation to chronic left ventricular overload. In those cases in which normal circulatory dynamics can no longer be reestablished, the heart can adapt itself (1) by maintaining an abnormally low cardiac output and a normal or near normal left ventricular filling pressure; and (2) by preserving a normal cardiac output at the expense of continued increase of left ventricular filling and left atrial pressures. The latter group of cases represents chronic left ventricular failure and is analogous to mitral stenosis in that a stimulus is provided for the frequent development of increased pulmonary vascular resistance, with its restricting influence upon cardiac output. The clinical implications of these findings are discussed.

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Phonocardiography in Ventricular Septal Defect*

Correlation Between Hemodynamics and Phonocardiographic Findings

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THIS investigation was carried out in order to evaluate the role of phonocardiography in estimating the degree of pulmonary hypertension in isolated ventricular septal defects.

MATERIAL AND METHODS

An auscultatory and phonocardiographic study was made of forty patients with isolated ventricular septal defect. The clinical diagnosis was established in all cases by cardiac catheterization and was confirmed by surgery in six patients and by postmortem examination in six cases.

An increase of 1.5 vol. per cent or greater in oxygen saturation at the ventricular level in comparison with an average right atrial oxygen saturation was present in every patient. Patients with pulmonary stenosis or atrial septal defect in addition to ventricular septal defect were not included. Patients with so-called Eisenmenger's complex are included. Hemodynamically they behave as do patients with ventricular septal defect, severe pulmonary hypertension and bidirectional shunt.

A pressure gradient from 10 to 35 mm. Hg across the pulmonary valve was considered to be due to hypertrophy of the right ventricular outflow tract or to high pulmonary flow rate rather than to organic pulmonary stenosis. There were seven such cases. Four of these patients underwent surgery and no organic pulmonary stenosis was found.

The forty patients were placed in three groups, arbitrarily divided by the ratio of right ventricular to peripheral artery pressure [*1*].

The correlation between pulmonary pressure and systemic pressure was grouped in the following manner [*1*]. Group I, normal or mild pulmonary hypertension, pulmonary artery pressure 20 to 40 per cent of systemic pressure. Group II, pulmonary artery pressure 40 to 70 per cent of systemic pressure. Group III, pulmonary artery pressure above 70 per cent of systemic pressure.

In group I, the pulmonary artery systolic pressure varied from 25 to 40 mm. Hg, in group II, from 40 to 60 mm. Hg and in group III it was higher than 60 mm. Hg ranging from 60 to 140 mm. Hg. Right ventricular and pulmonary artery pressures were determined during routine right heart catheterization using a Statham strain gauge (T-23D) with zero point at half the chest diameter at the sternal angle. The cardiac output, pulmonary flow and total pulmonary resistance were determined using the formulas presented elsewhere [*2,3*].

The Sanborn Twin Beam phonocardiograph was used in every case. In cases presenting a special problem a four channel Visocorder (Honeywell) modified for sound recording was used. Tracings were taken at a paper speed of 75 mm. per second.

A logarithmic recording technic for accurate analysis of high frequency sound was used in all cases [*4-6*]. The stethoscopic recording technic was used in addition at the apex and left sternal border areas in order to detect low frequency sounds such as third and fourth sounds. The sound tracings were recorded at the apex, left sternal border, at the third and fourth intercostal spaces, pulmonary and aortic areas.

Electrocardiographic tracings were used in order to identify the atrial sound. The carotid tracing, jugular venous tracing and apexcardiogram were recorded simultaneously with the phonocardiogram using a crystal piezo electric microphone pickup (Sanborn).

In the majority of cases two simultaneous sound tracings in different precordial areas were also obtained. The tracings were analyzed in the usual manner but special attention was given to the splitting of the second sound and its relation to the respiratory cycle, duration and accentuation of systolic murmur, and duration of right ventricular systole. The components of the split second sound were identified by their relation to the dicrotic notch of the carotid tracing. The aortic component of the second sound usually preceeded the dicrotic notch by .02 to .03 sec-

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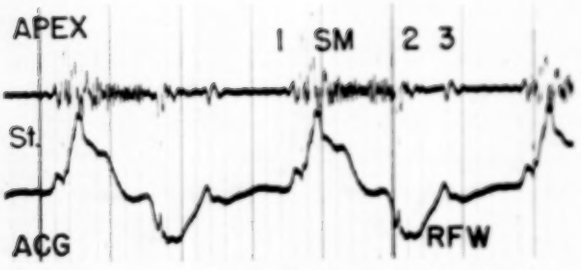

FIG. 1. Patients with ventricular septal defect without pulmonary hypertension. Group I (pulmonary artery pressure 24/8 mm. Hg; pulmonary flow 7.5 L./minute; systemic flow 2.1 L./minute). Pansystolic murmurs with third heart sound coincident with rapid filling wave of the apexcardiogram. (VSD = ventricular septal defect, ACG = apexcardiogram, ST = stethoscopic recording, RFW = rapid filling wave).

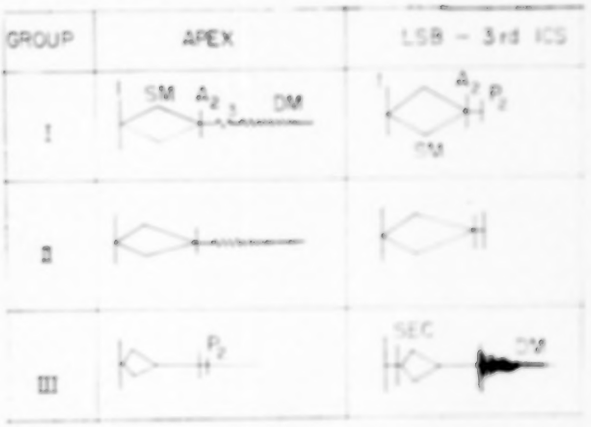

FIG. 2. Graphic representation of the phonocardiographic findings in patients with ventricular septal defect. (See text.) Group I, pulmonary artery pressure 20 to 40 per cent of systemic pressure. Group II, pulmonary artery pressure 40 to 70 per cent of systemic pressure. Group III, pulmonary artery pressure above 70 per cent of systemic pressure.

ond (pulse wave transmission from the aortic valve to the carotid artery). The pulmonary component of the second sound was recognized by its occurrence after the dicrotic notch of the carotid tracing and by its greater intensity at the pulmonary area. This concept was not valid in patients with moderate and severe pulmonary hypertension since the pulmonic second sound was so closely split that the only way to differentiate the two components was by the use of simultaneous sound tracing at the apex and pulmonary area.

The criteria of Leatham and Vogelpoel [7] were used to identify the systolic ejection click.

The duration of right ventricular systole was determined from simultaneous sound tracings taken at the tricuspid and pulmonary areas. The interval was calculated from the tricuspid component of the first sound at the tricuspid area to the pulmonic component of the second sound at the pulmonary area [8]. Left ventricular systole was measured from the mitral component of the first sound to the aortic component of the second sound.

Systolic and diastolic murmurs were graded according to the criteria of Freeman and Levine [9] graded from 1 to 6. All patients were examined by three different observers and the murmurs were graded independently.

RESULTS

Group I. There were fourteen patients in this group. All had normal or slightly elevated pulmonary pressure ranging from 25 to 40 mm. Hg (pulmonary artery pressure 20 to 40 per cent of systemic pressure). Usually these were asymptomatic patients in whom a cardiac murmur was heard during a routine physical examination. Cardiac catheterization demonstrated a left-to-right shunt at the ventricular level with increased pulmonary flow and normal pulmonary resistance. The pulmonary vascular resistance in this group varied from 200 to 500 dynes/sec./cm^5.

The first sound was normal in all patients and no systolic ejection click was recorded. A third sound was present in eight patients (57 per cent) in whom there was markedly increased pulmonary flow. (Fig. 1.) A fourth sound was present in only two patients (14 per cent) and in both the right auricular pressure was within normal limits.

The second sound was split at the pulmonary area and a slight change in the width of the split could be demonstrated during the respiratory cycle. The A_2-P_2 interval was .06 second in one case, .05, .04 and .03 second in four cases, respectively. The intensity of the two components of split second sound could not be measured directly. However, their intensity could be compared from their amplitude in logarithmic recording technic [8]. From this analysis the pulmonic component of the second sound was considered to be accentuated in only two cases. In the other twelve cases it was judged to be within normal limits. In all cases, a high frequency, high amplitude pansystolic flow murmur could be recorded at the left sternal border at the third and fourth intercostal spaces, well transmitted to all precordial areas. (Fig. 2.) It was considered by auscultation to be grade 4 to 5 in eleven cases (78 per cent) and grade 3 in only three cases. These murmurs started immediately after the first sound and ended at the aortic component of the second sound in all

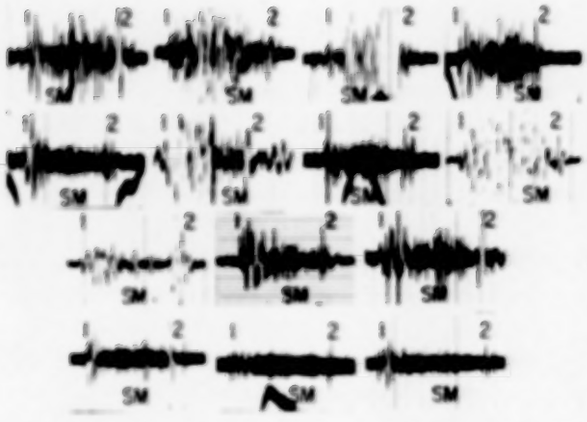

FIG. 3. Systolic murmur in fourteen patients with ventricular septal defect without pulmonary hypertension (group I). Sound tracings taken at the left sternal border. Fourth intercostal space with logarithmic technic. Shows a high amplitude pansystolic murmur. (See text.)

FIG. 4. Patient with ventricular septal defect with moderate pulmonary hypertension. Group II (pulmonary artery pressure 65/25 mm. Hg; femoral artery pressure 120/75 mm. Hg). *Top*, before surgery. Pansystolic murmur with mid-systolic accentuation. Medium frequency diastolic murmur. *Bottom*, one month after surgery. No murmur was recorded.

cases. (Fig. 3.) In all but one, the murmur showed mid-systolic accentuation. (Table I.) In five cases a distinct low pitched diastolic rumble without presystolic accentuation was heard and recorded at the apex and was assumed to be due to increased mitral flow. (Fig. 4, top.)

In one case a high pitched diastolic decrescendo murmur was recorded at the left sternal border. In this patient there was no evidence of pulmonary hypertension and this murmur was considered to be due to aortic incompetence [*10–11*].

The jugular venous tracing was considered to be normal in all cases. (Fig. 5, top.) Right ventricular systole ranged from .25 to .44 second. (Table II.)

Group II. Seven patients were studied in this group. Cardiac catheterization revealed a moderately elevated pulmonary pressure, 40 to 60 mm. Hg (40 to 70 per cent of systemic pressure), increased pulmonary flow and pulmonary resistance and a left-to-right shunt at the ventricular level. No right-to-left shunt at rest could be demonstrated in these patients. The pulmonary vascular resistance varied from 300 to 900 dynes/sec./cm^5.

The first sound was normal in all cases and was followed by systolic ejection click in only one case in which x-ray studies demonstrated a dilated pulmonary artery; the pulmonary artery pressure was 60/15 mm. Hg.

A third sound was recorded in two cases and a fourth sound was present in one. The second sound was closely split at the pulmonic area and the A_2-P_2 interval in expiration was .04 second in five cases and .03 second in two. No significant change in the width of the split of the second sound could be demonstrated during inspiration. The pulmonic component of the

TABLE I
TIME ACCENTUATION OF THE SYSTOLIC MURMUR IN VENTRICULAR SEPTAL DEFECT
(No murmur showed late systolic accentuation)

Group	Time Accentuation of Systolic Murmur	
	Early	Middle
I	1	13
II	2	5
III	15	4

TABLE II
DURATION OF RIGHT AND LEFT VENTRICULAR SYSTOLE IN VENTRICULAR SEPTAL DEFECT

Group	Duration of Right Ventricular Systole		Duration of Left Ventricular Systole	
	Range (sec.)	Average (sec.)	Range (sec.)	Average (sec.)
I	.25–.44	.31	.24–.44	.30
II	.28–.34	.31	.28–.34	.28
III	.22–.34	.29	.24–.36	.29

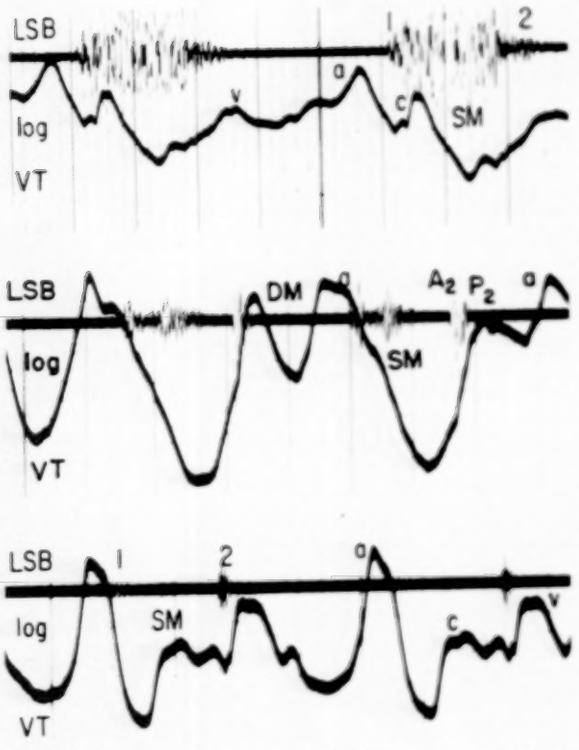

FIG. 5. *Top*, patients with ventricular septal defect without pulmonary hypertension. Group I, pulmonary artery pressure 30/15 mm. Hg; pulmonary flow 7.3 L./minute. A pansystolic murmur is recorded at the left sternal border. Venous tracing shows normal "a" waves. *Middle*, patients with ventricular septal defect with moderate pulmonary hypertension. Group II, pulmonary artery pressure 70/35 mm. Hg. Systolic murmur with early and mid-systolic accentuation ending .06 second before the second sound. Venous tracing shows prominent "a" waves. *Bottom*, patients with ventricular septal defect with severe pulmonary hypertension. Group III, pulmonary artery pressure 110/30 mm. Hg. Low amplitude, early systolic murmur. Venous tracing shows giant "a" waves.

second sound was considered to be accentuated in five cases in which a comparative height in logarithmic tracing at the pulmonary area revealed a pulmonic component higher than the aortic component. The relationship was approximately 2:1.

The systolic murmur in this group was somewhat different from that in group I. (Fig. 6.) It was judged to be grade 5 in only two cases and grade 3 or 4 in five. This murmur started immediately after the first sound in all but one case and ended at the aortic component of the second sound in four cases. In the other three cases it ended .03 to .08 second before the second sound.

A diastolic apical murmur was recorded in four cases. (Fig. 7.)

The venous tracing showed prominent "a"

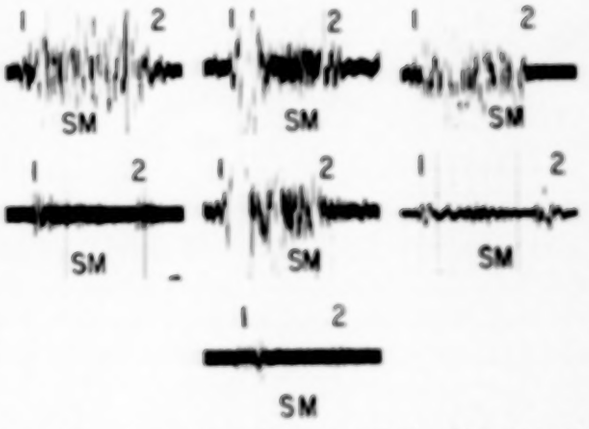

FIG. 6. Systolic murmurs in seven patients with moderate pulmonary hypertension (group II). The sound tracings were taken at the left sternal border fourth intercostal space with logarithmic technic. Systolic murmur ending before or at the second sound. (See text.)

waves in two cases. (Fig. 5, middle.) The right ventricular systole ranged from .28 to .34 second. (Table II.)

Group III. Nineteen patients were studied in this group to which belonged patients with severe pulmonary hypertension in whom the pulmonary pressure was higher than 60 mm. Hg (above 70 per cent of peripheral pressure).

Cardiac catheterization revealed an increased pulmonary resistance, slightly elevated pulmonary flow, a left-to-right shunt and in some cases a bidirectional shunt. The pulmonary vascular resistance varied from 800 to 3,600 dynes/sec./cm^{-5}. Twelve patients presented a bidirectional shunt, and in seven, only a left-to-right shunt.

By auscultation the systolic murmur was considered to be grade 4 in four cases and grade 2 to 3 in fifteen cases. A normal first sound was present in all cases. A systolic ejection click was recorded in five cases (38 per cent) in which a dilated pulmonary artery could be identified by radiological studies. (Fig. 8.) A third sound was recorded in only two instances. No fourth sound was present.

The second sound was closely split at the pulmonary area and no significant change in duration of the split could be demonstrated during the inspiration. The A_2-P_2 interval was considered to be .03 second in one case, .02 second in sixteen cases and in two cases it was recorded simultaneously with the aortic component and the duration of the split could not be measured. The pulmonic component of the second sound was accentuated in all cases and the relationship

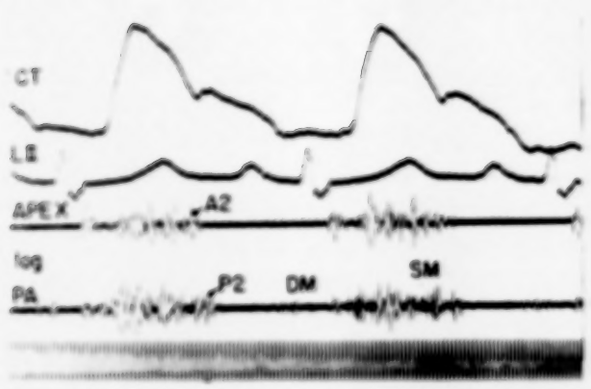

FIG. 7. Patient with ventricular septal defect without pulmonary hypertension. Group I, pulmonary artery pressure 40/25 mm. Hg; femoral artery pressure 108/84 mm. Hg; pulmonary flow 4,293 cc./minute; systemic flow 1,512 cc./minute; pulmonary resistance 522 dynes/second/cm^{-5}. Systolic murmur beginning .03 second after the first sound and ending at the aortic component of second sound. Pulmonic component of second sound is slightly accentuated.

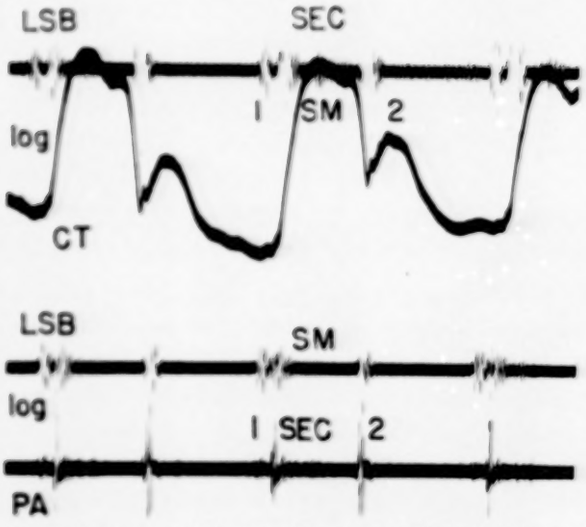

FIG. 8. Patient with ventricular septal defect with severe pulmonary hypertension. Group III, pulmonary artery pressure 80/40 mm. Hg; femoral artery pressure 85/50 mm. Hg. *Top*, systolic ejection click. (SEC.) Mid-systolic murmur ending .07 second before the second sound. Second sound is closely split (.02 second) and the pulmonic component is accentuated. *Bottom*, simultaneous sound tracing in the same patient. The systolic ejection click is best recorded at the pulmonic area.

FIG. 9. Patient with ventricular septal defect with severe pulmonary hypertension. Group III, pulmonary artery pressure 100/150 mm. Hg; femoral artery pressure 120/75 mm. Hg; pulmonary flow 2.3 L./minute; pulmonary resistance 2.376 dynes/second/cm^{5}. Simultaneous phonocardiogram, *Top*, with right atrial pressure curve. *Bottom*, with pulmonary artery pressure. Low amplitude systolic murmur and a pulmonary diastolic murmur. Giant "a" in right atrial pressure tracing. Accentuated pulmonary second sound coincident with the dicrotic notch of pulmonary artery tracing.

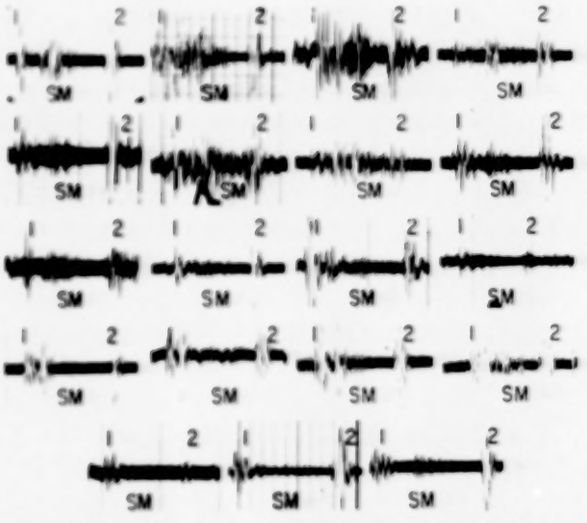

FIG. 10. Systolic murmur in nineteen patients with ventricular septal defect with severe pulmonary hypertension (group III). The sound tracing was taken at the left sternal border fourth intercostal space with logarithmic technic. Systolic murmur with early and or mid-systolic accentuation ending before the second sound. (See text.)

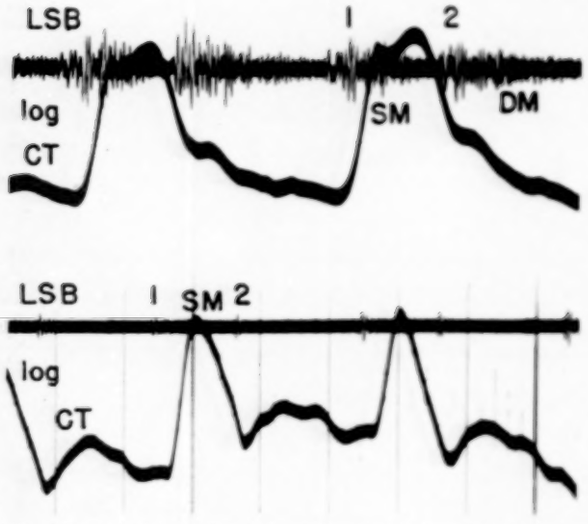

FIG. 11. Patient with ventricular septal defect with severe pulmonary hypertension. Group III, pulmonary artery pressure 91/12; femoral artery pressure 90/52 mm. Hg; pulmonary resistance 1,065 dynes/second/cm^{-5}. *Top*, before surgery. Early decrescendo systolic murmur. Pulmonary diastolic murmur. *Bottom*, one week after surgery. Low amplitude systolic murmur. The diastolic murmur is no longer present.

between P_2-A_2 was 2 to 3:1. A low amplitude, medium frequency, systolic murmur was recorded at the left sternal border at the third and fourth intercostal spaces. (Fig. 9.) In many of these patients it assumed the configuration of an ejection murmur. It started immediately after the first sound in eleven cases and in eight cases the interval from the mitral first sound to the beginning of the murmur varied from .02 to .08 second. This murmur extended to the aortic component of the second sound in only three cases. An interval from the end of the murmur to the aortic second sound which varied from .04 to .10 second was present in sixteen cases. In no case was a pansystolic murmur (as was present in group I) recorded. (Fig. 10.)

A diastolic apical murmur was heard or recorded in twelve cases (63 per cent) and a diastolic murmur of pulmonary insufficiency (Graham-Steell murmur) was recorded in ten cases (55 per cent). (Fig. 11.) In patients with diastolic apical murmur a bidirectional shunt was confirmed by catheterization but the left-to-right shunt was dominant. In no case with dominant right-to-left shunt was a diastolic murmur at the apex recorded. The jugular venous tracing showed giant "a" waves in five cases, tall "a" waves in ten cases and was normal in four cases. (Fig. 5, bottom.)

TABLE III

SUMMARY OF AUSCULTATORY AND PHONOCARDIOGRAPHIC FINDING IN VENTRICULAR SEPTAL DEFECT

Phonocardiographic Findings	Group I	Group II	Group III
First sound	Normal	Normal	Normal
A_2-P_2 interval (sec.)	.03 to .06	.02 to .04	.00 to .02
Pulmonic second sound	Normal	Slight accentuation	Marked accentuation
Systolic ejection click	No	No	Common
Third sound	Common	No	No
Fourth sound	Rare	No	No
Intensity of systolic murmur	V to VI	III to V	I to III
Duration of systolic murmur	Pansystolic	Proto- & Mid-systolic	Protosystolic
Accentuation of systolic murmur	Midsystolic	Early mid-systolic	Early
Diastolic apical murmur	Common	Common	Uncommon
Pulmonary diastolic murmur	No	Uncommon	Common
Duration of right ventricular systole (sec.)	.25 - .44	.28 - .34	.22 - .34

The right ventricular systole ranged from .22 to .34 second. (Table I, Fig. 12.)

COMMENTS

Phonocardiography, from this study, seems to be a useful method for assaying ventricular septal defect and evaluating the degree of pulmonary hypertension. (Table III.)

The first sound is usually normal in patients with ventricular septal defect (provided right bundle branch block is not present; if right bundle branch block is present, there is a delay in the closure of the tricuspid valve). In our series the first sound was normal in all three groups and in no case was a complete right bundle branch block present. Delayed closure of pulmonary valve produced a split second sound which is not as wide as is seen in cases of atrial septal defect [*8,15*] or pulmonary stenosis [*16*]. The pulmonic component of the second sound was normal in all cases in group I. However, the width of the split did not change significantly in inspiration.

The duration of right and left ventricular systole is unequal in patients with ventricular septal defects. In our series, right ventricular systole was .01 to .03 second longer than the left ventricular systole and this interval was constant during the respiratory cycle. (Table I.) Patients with ventricular septal defect without pulmonary hypertension who have slight prolongation of right ventricular systole, increased pulmonary flow, and relative incapacity to increase pul-

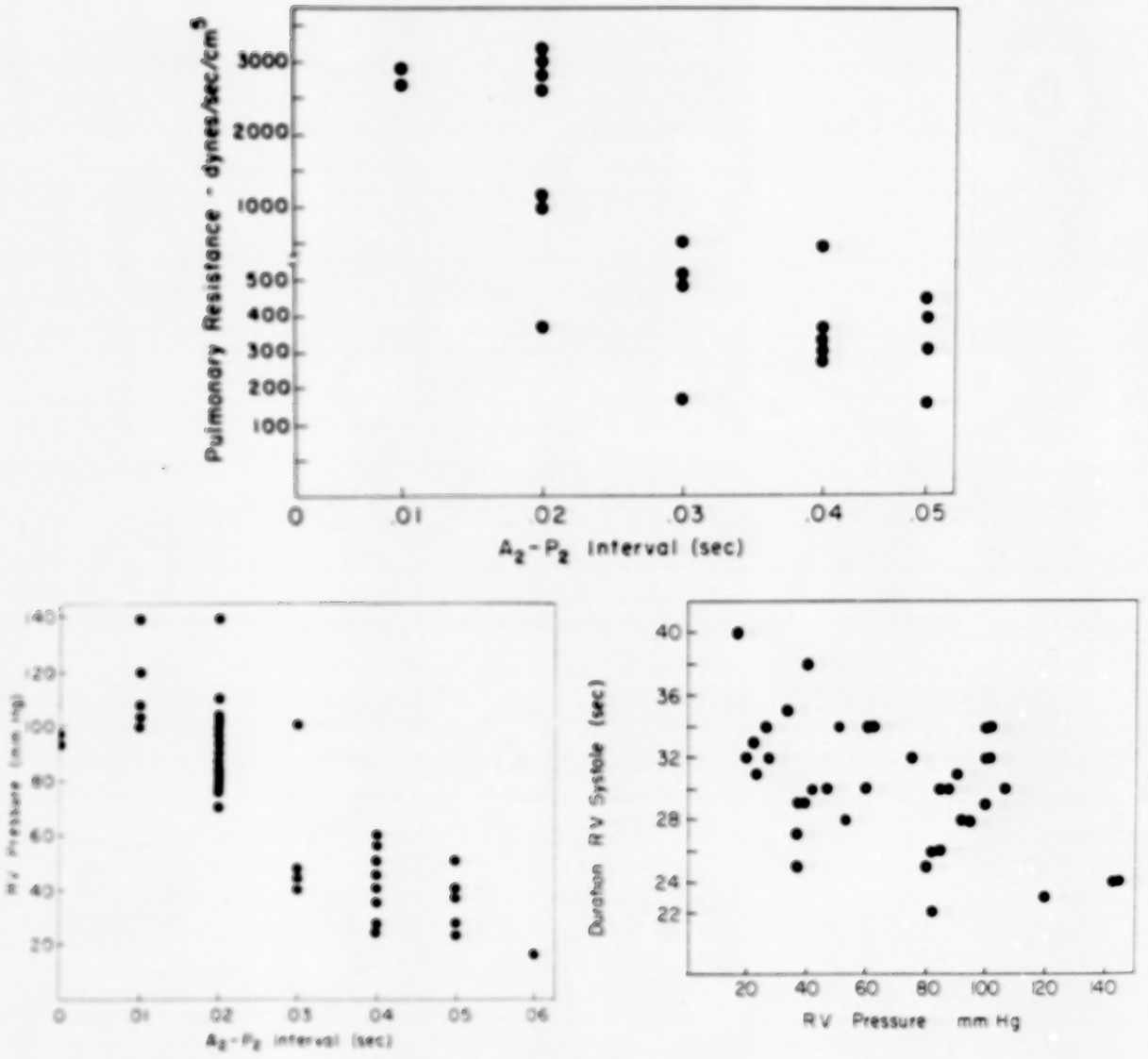

FIG. 12. *Top*, correlation between the split second sound (A_2-P_2 interval) and pulmonary vascular resistance. *Left*, correlation between the split second sound and the right ventricular pressure. *Right*, correlation between the duration of right ventricular systole and the right ventricular pressure. (See text.)

monary flow during inspiration are unable to increase the width of the split during the inspiratory phase of respiratory cycle. This is similar to the observation which has been made in atrial septal defect [*17*].

In patients with severe pulmonary hypertension and bidirectional shunt the pulmonary flow is normal or only slightly increased. The high pulmonary artery diastolic pressure and pulmonary vascular resistance may be responsible for the early closure of the pulmonary valve [*20,21*]. (Fig. 12.) These patients are unable to increase the duration of right ventricular systole during inspiration and a closely split second sound with respiratory fixation may be expected [*22,23*]. In some patients with severe pulmonary hypertension the right ventricular systole is so short and the pulmonary valve closes so early that a paradoxical split of the second sound may be expected. In Figure 13 the two components of the second sound preceded the dicrotic notch of the carotid tracing and the simultaneous tracing taken at the apex and pulmonic area showed a louder vibration occurring before the aortic second sound (reverse split).

A third sound was recorded in eight cases in group I and in two cases in group III. These patients with a third sound presented a high

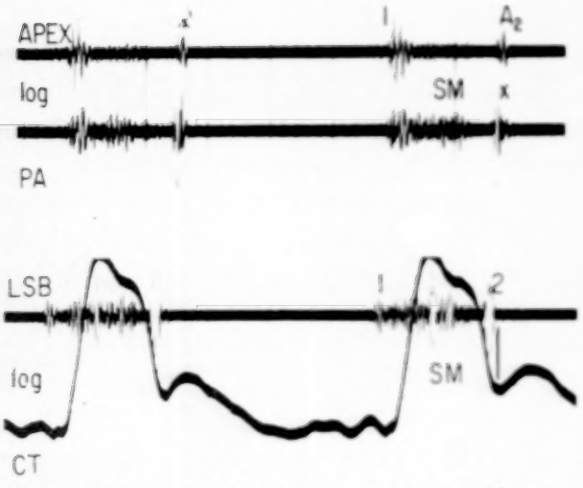

FIG. 13. Patients with ventricular septal defect with severe pulmonary hypertension and bidirectional shunt. Group III, pulmonary artery pressure 120/45 mm. Hg. *Top*, simultaneous sound tracing at the apex and pulmonic area shows the loudest vibrations (x) occurring at the pulmonic area proceeding the second sound at the apex. (reverse split.) The vibration of the pulmonary second sound actually crosses the apex recording (x'). *Bottom*, both components of second sound occur before the dicrotic notch in the carotid tracing.

pulmonary flow (6 to 10 L./minute), this being two to four times the systemic flow. An electrocardiographic analysis in these patients revealed the typical pattern of diastolic overload of the left ventricle [*33,34*]. In this situation a rapid left ventricular diastolic filling period can be expected which may account for the presence of a third sound. Simultaneous sound tracing at the apex with a left ventricular apex phonocardiogram revealed that the third sound was in all cases coincident with the peak of rapid filling phase. (Fig. 1.)

Patients with moderate and severe pulmonary hypertension in whom the pulmonary flow was normal or slightly elevated did not present a third sound. Electrocardiographic studies in this group did not reveal the typical pattern of diastolic overload of the left ventricle. Therefore the presence of a third sound in the absence of heart failure in patients with ventricular septal defect seemed to indicate normal or only slightly elevated pulmonary pressure and pulmonary flow greater than systemic flow. A fourth sound was recorded in two cases in group I, in one case in group II and in none in group III.

A systolic ejection click was present in eight cases in group III, in one case in group II and in none in group I. In all cases in which the systolic ejection click was recorded there was moderate dilatation of the pulmonary artery which may account for its presence [*7,21*]. It seemed to be associated with a marked degree of pulmonary hypertension.

The systolic murmur is the most striking auscultatory and phonocardiographic finding in patients with ventricular septal defect [*25,36*]. It has a special characteristic which permitted an observer to evaluate the degree of pulmonary hypertension. (Fig. 2.) Patients without pulmonary hypertension (group I) presented a loud grade 4 to 5 pansystolic murmur at the left sternal border at the third or fourth intercostal space which was well transmitted to all precordial areas. It was judged to be due to blood flow across the defect which began immediately after the atrioventricular valve closure and ended at the semilunar valve closure [*27,35*].

As pulmonary hypertension developed the amount of left-to-right shunt decreased. With decrease in the shunt there was an associated diminution in the intensity of the systolic murmur and in its duration. As the right ventricular pressure approaches the systemic pressure and a common ejection force occurs in both ventricles, a small bidirectional shunt occurs which may be difficult to determine by cardiac catheterization. In such cases the systolic murmur is usually only grade 1 to 2 in intensity. In addition, the murmur is noted to end .04 to .10 second before the aortic component of the second sound in group III. It is possible that at the beginning of systole the left ventricular pressure may be slightly higher than the right ventricular pressure producing a small left-to-right shunt. When the right ventricular pressure equals the left ventricular pressure the left-to-right shunt disappears or becomes insignificant. Patients with dominant right-to-left shunt also have a low amplitude short systolic murmur.

A diastolic apical murmur was recorded in patients with increased pulmonary flow. It was believed to be due to turbulence and high flow across the mitral valve [*28*]. This diastolic murmur was infrequent in patients with moderate and severe pulmonary hypertension with dominant right-to-left shunt. A pulmonary diastolic murmur was recorded in ten patients with severe pulmonary hypertension and was attributed to pulmonary valve insufficiency [*18,29*].

The role of pulmonary hypertension in the genesis of the pulmonary diastolic murmur due to pulmonary valve insufficiency is well demon-

strated by the effect of intravenous injection of reserpine. In these patients a significant fall in pulmonary pressure is accomplished immediately after injection and the diastolic murmur disappears [*30,31*].

Reinhold and Nadas [*32*] stated that the presence of an apical presystolic murmur correlated well with the size of the defect but they did not mention if these patients presented pulmonary hypertension. In none of our patients with a diastolic apical murmur was a presystolic murmur recorded.

The jugular venous tracing was also of some help in differentiating the three groups. In patients with normal pulmonary pressure the venous tracing was normal in all cases. In patients with moderate pulmonary hypertension tall "a" waves were recorded in only two instances. However, in patients with severe pulmonary hypertension "giant" or tall "a" waves were recorded in fifteen instances (78 per cent) suggesting that the right auricle is under strain in severe pulmonary hypertension. (Fig. 5.)

SUMMARY AND CONCLUSIONS

1. An auscultatory and phonocardiographic study was made in forty patients with isolated ventricular septal defect and correlated with the hemodynamic findings.

2. In patients with normal or slightly elevated pulmonary pressure a loud pansystolic flow murmur at the left sternal border was recorded in all cases and was attributed to blood flow through the septal defect. With increments in pulmonary hypertension the systolic murmur became less intense. In all patients with severe pulmonary hypertension a faint systolic murmur was present which was usually grade 2 with maximal intensity at the beginning of systole.

3. The duration of the split second sound with accentuation of the pulmonic component was a good index of the degree of pulmonary hypertension. An A_2-P_2 interval less than .03 second suggested moderate to severe pulmonary hypertension This was judged to be caused by increased diastolic pressure in the pulmonary artery associated with marked increase in pulmonary resistance with consequently shortening of right ventricular systole.

4. A third sound was frequently present in patients with moderate left-to-right shunt, increased pulmonary flow and a normal or slightly elevated pulmonary pressure. Patients with moderate and severe pulmonary hypertension did not present third sounds. It was assumed to be due to diastolic overload of the left ventricle.

5. The presence of a systolic ejection click indicated a marked degree of pulmonary hypertension with dilatation of the pulmonary artery.

6. A pulmonary diastolic murmur was found to be suggestive of severe pulmonary hypertension with pulmonary insufficiency.

7. A mid-diastolic rumble without presystolic accentuation was recorded and attributed to increased flow through the mitral valve in twenty-one patients with marked left-to-right shunt. Patients with pulmonary hypertension and dominant right-to-left shunt did not present a mitral diastolic murmur.

8. The presence of a giant "a" waves in the jugular venous tracing indicates the presence of severe pulmonary hypertension and was attributed to the increased resistance to right atrial emptying and not true right atrial hypertension.

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Senile Cardiac Amyloidosis*

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First described by Virchow [*1*] in 1857, amyloid deposition in the heart was termed "senile amyloid" nineteen years later by Soyka [*2*], who recognized it as an abnormality particularly prone to occur in aged persons. Since that time many examples of cardiac amyloidosis have been recorded [*3–17*], invariably in persons more than fifty years of age. In 1948 King [*10*] reported five instances of amyloidosis of this variety in patients in the ninth and tenth decades, and used the expression "atypical amyloidosis, associated with senility." In 1950 Jones and Frazier [*13*] reported that "atypical" amyloidosis, primarily involving the heart and blood vessels, occurred with unusual frequency in people living in Western Tennessee. An incidence of 2.33 per cent was noted in 600 consecutive necropsies on adults. All these cases were encountered in persons over the age of fifty years; the incidence in this group was 3.47 per cent. It was predicted that when the clinical pattern and pathologic lesions became more familiar, a similar incidence would be found in other geographic areas. In 1952 Josselson, Pruitt and Edwards [*14*] reported twenty-nine cases in which amyloidosis was localized in the heart, with insignificant distribution in other organs. Nineteen of these twenty-nine instances had been recognized on routine pathologic examination. An additional ten examples were found as the result of a purposeful survey of sections from 600 necropsies. One hundred men and 100 women were studied in each of the seventh, eighth and ninth decades. They found no cases in the seventh decade, three in the eighth, and seven in the ninth. Eight of the ten cases occurred in men. In 1955 Hüsselmann [*16*] reported seventy-six examples of amyloid deposition in the heart; sixty-nine of these represented "senile cardiovascular amyloidosis" in patients aged seventy years or older.

At the Cincinnati General Hospital, a municipal general hospital, a remarkable number of cases of amyloidosis were encountered at necropsy during the five years between 1953 and 1957. These were characterized by occurrence in aged persons and predominant deposition in the heart. Prior to this time only four examples of this variety of amyloidosis had been recorded in the diagnostic files, which included some 22,000 necropsy records. The present investigation was performed to determine the incidence of senile cardiac amyloidosis and to ascertain whether its incidence has increased in recent years.

MATERIALS AND METHODS

Two four-year periods were selected for comparative study: Period I, 1941 to 1944; period II, 1953 to 1956. Period I represented the most recent four-year period for which records were complete. Period II was selected because no cases of cardiac amyloidosis were recorded in the diagnostic files, but the material was sufficiently recent to anticipate that tissue sections and clinical and necropsy records would be adequate and readily available. Since our recent examples of the lesion under consideration and those reported by others [*3–17*] had occurred almost exclusively in aged persons, the survey was restricted to patients fifty-five years of age and older.

All sections of heart stored in the files (at least two in each case) from necropsy examinations performed during the two periods selected were re-examined and screened by one of us (L. B.). Those sections with hyaline deposits that could conceivably represent amyloid were then critically evaluated by both of us. Examples of hyaline substance considered to be at all suggestive of amyloid were stained with acidified crystal violet [*18*] to substantiate the presence of amyloidosis. In most cases the diagnosis was obvious on examination of conventionally stained sections and the crystal violet stain was merely confirmatory.

Among the lesions considered equivocal when stained with hematoxylin and eosin, one-third proved

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FIG. 1. Cut surface of ventricular myocardium from a patient with severe (4 plus) amyloidosis. Note waxy appearance.

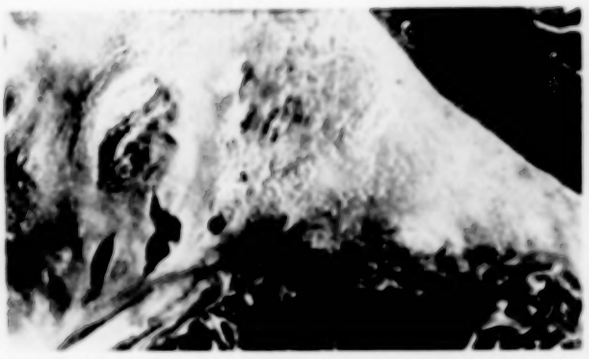

FIG. 2. Endocardial surface of atrium from a patient with cardiac amyloidosis. Note miliary translucent nodules of amyloid just beneath endocardium.

to be orthochromatic (negative) with the crystal violet stain. However, in all of these, interstitial hyalin was present in only minimal amounts. In all instances in which large quantities of hyaline deposit resembling amyloid were detected the confirmatory stains proved to be positive. In the entire group of cases in which the diagnosis of cardiac amyloidosis was established, all available microscopic sections from other viscera were reviewed in order to exclude amyloid deposition of varieties other than that termed the senile cardiac variety. The sections of viscera containing hyaline deposition resembling amyloid also were stained with crystal violet. Finally, the clinical and necropsy records of those cases in which amyloidosis was conclusively demonstrated were systematically reviewed and pertinent information tabulated. (Tables I to VII.)

RESULTS

In the age group selected, 986 necropsies were performed during period I; in period II, there were 1,325 examinations. Forty-two instances of senile cardiac amyloidosis were detected. Only seventeen of these had been recognized at the time of original examination; in twenty-five instances amyloid had not been detected.

Amyloid was deposited interstitially in the myocardium, beneath the epicardium and endocardium, and in the heart valves. When it had accumulated in substantial amounts a peculiar rigidity was imparted to the tissue and the classic waxy or lardaceous appearance was manifest. (Fig. 1.) Subendocardial deposits, especially in the atria, were often focal in distribution and were characterized by translucent miliary nodules. (Fig. 2.) Occasionally, similar fine nodularity was encountered beneath the endocardium of the ventricles or beneath the epicardium. (Fig. 3.) Iodine solution applied to the affected surface gave the mahogany brown coloration of amyloid. (Fig. 4.)

In none of the protocols related to earlier cases was there mention of the use of this technic. However, in instances of severe cardiac amyloidosis encountered since 1956, application of iodine solution invariably highlighted the major deposits.

A breakdown by decades revealed an increasing incidence of cardiac amyloidosis with age ($P = .001$). (Table I.) While there was only one subject with the disorder among patients in the seventh decade, there were eight in forty-two in the tenth decade. A comparison of the relative incidence in the two four-year periods shows a similar percentile incidence in all decennial cohorts but the tenth. In this cohort there were no examples of amyloidosis in ten necropsies during period I whereas eight examples appeared in thirty-three necropsies during period II ($P = .005$). This rise in incidence in the oldest age group resulted in an increase in over-all incidence in all cases examined from 1.22 to 2.26 per cent in the reviewed test periods, or an increase in over-all incidence in the entire adult autopsy population (over twenty-one years of age) in these periods from 0.66 to 1.52 per cent. (Table I.) However, this difference in incidence is not of definite statistical significance ($P > .05$).

The distribution of senile cardiac amyloidosis according to sex and race is shown in Table II. The lesion appeared in women and Negroes with slightly higher frequency, the greatest incidence being in Negro women. However, statistical analysis revealed that the differences were not significant ($P > .05$). In effect, this would indicate that the incidence is not influenced by race or sex.

FIG. 3. Outer surface of left auricular appendage from a patient with cardiac amyloidosis involving epicardium. Miliary translucent nodules of amyloid are clearly visible.

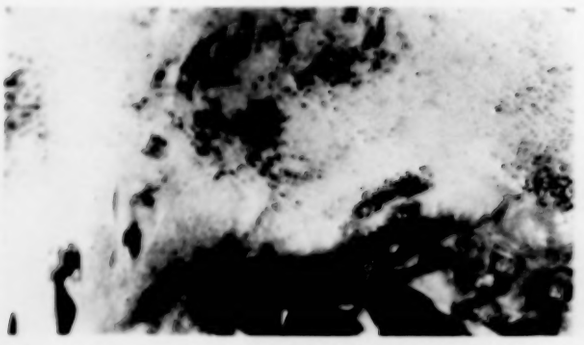

FIG. 4. Same case as Figure 2. Lugol's solution and dilute acid have been applied to the atrial endocardium, with typical mahogany brown coloration of miliary amyloid deposits.

It is not the prime purpose of this study to discuss the microscopic features of amyloid deposits in the myocardium. Larsen [*6*] believed that the substance was deposited primarily about venocapillary endothelium from which it extended to infiltrate the adjacent parenchyma. He further stated that amyloid might gain entrance into occasional cardiac muscle cells by a process of invagination. We have not observed this phenomenon; amyloid always appeared as an interstitial deposit, causing compression and atrophy of myocardial fibers in the more advanced lesions. (Figs. 5, 6, 7 and 8.) Jones and Frazier [*13*], on the other hand, indicated that amyloid was more closely related to reticulum than to capillaries. In our cases perivascular localization was not a feature in the heart, but was encountered in other regions.

The amount of amyloid deposit varied widely. (Figs. 5, 6, 7 and 8.) The involvement of the same heart might differ from region to region to a considerable extent. Such variation has been manifest on occasion in more recent cases in which the lesion has been recognized grossly. An estimate of the amount of amyloid deposited in a given heart on the basis of examination of a

TABLE 1

AGE DISTRIBUTION OF CARDIAC AMYLOIDOSIS

Age (yr.)	1941–1944			1953–1956		
	No. of Autopsies	Cases of Amyloidosis	Per cent Incidence	No. of Autopsies	Cases of Amyloidosis	Per cent Incidence
55–59	182	0	0	171	0	0
60–69	376	0	0	431	1	0.23
70–79	310	5	1.6	467	7	1.5
80–89	108	7	6.4	223	14	6.3
90–99	10	0	0	33	8	24.2
Total	986	12	1.22	1325	30	2.26
Adults below 55 (>21)	824	..	....	647	..	....
Grand total (adults >21)	1,810	12	0.66	1,972	30	1.52

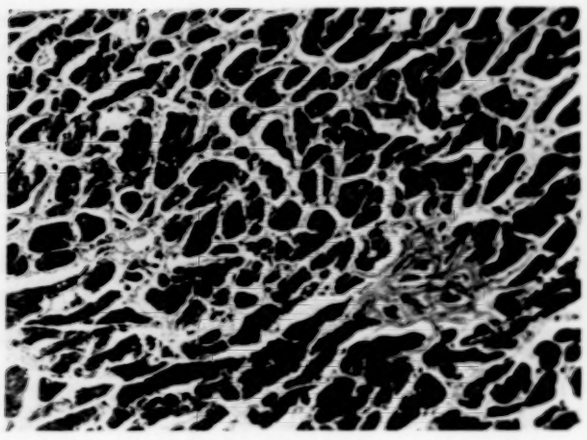

FIG. 5. Cardiac amyloidosis, 1 plus. A single focus of interstitial amyloid deposit is seen. Hematoxylin and eosin stain × 160.

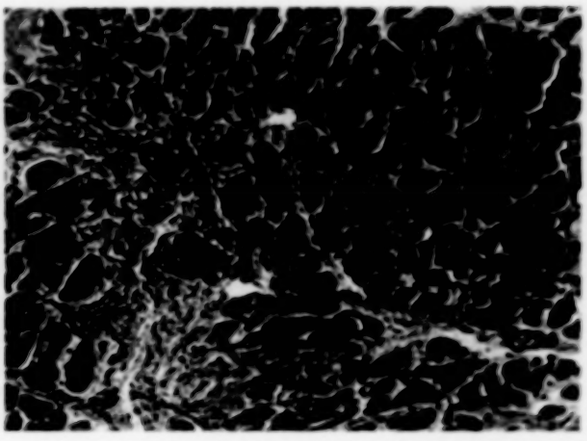

FIG. 6. Cardiac amyloidosis, 2 plus. There are several small foci of amyloidosis. The fibrillar strand to the left represents a mass of connective tissue. Hematoxylin and eosin stain × 160.

few sections may be grossly inaccurate in an individual instance. Nevertheless, such an estimate may have statistical validity when dealing with large numbers of cases. Indeed, there seemed reason to believe that the amount of myocardial dysfunction induced by the process might reflect the quantity of amyloid deposited in the ventricular myocardium.

Accordingly, a crude grading system for estimating the severity of the disease was devised (grade 1, replacement of 5 to 10 per cent myocardium; grade 2, 10 to 25 per cent; grade 3, 25 to 50 per cent; grade 4, over 50 per cent). (Table III.) Only in the group graded 4 plus did a majority of hearts weigh more than the average of the control subjects, but four of five of these subjects were found to have had hypertension. In addition, only in this group (4 plus) was the average weight greater than the average of a control group of forty-two identically aged subjects without cardiac amyloidosis. These observations would suggest that amyloid displaces rather than supplements myocardial substance. Indeed, cardiomegaly in most patients was found more likely to be a result of other cardiovascular disorders, such as hypertension, coronary arteriosclerosis or calcareous aortic stenosis, than of the amyloidosis. (Tables III and IV.)

In nineteen cases the weight of the heart exceeded the average of the control subjects; seven of these had hypertension and coronary arteriosclerosis in addition to amyloidosis; nine had severe coronary arteriosclerosis; one had coronary arteriosclerosis and severe anemia; and

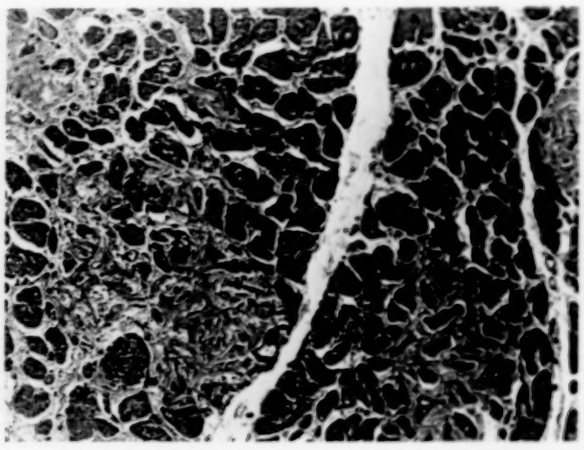

FIG. 7. Cardiac amyloidosis, 3 plus. All the hyaline interstitial material represents amyloid. Note that the deposit is extracellular but causes compression atrophy of myocardial fibers in involved areas. Hematoxylin and eosin stain × 160.

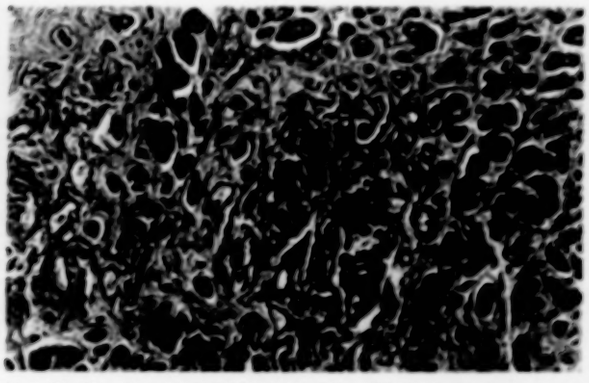

FIG. 8. Cardiac amyloidosis, 4 plus. Widespread replacement of the myocardium by amyloid deposit is manifest, but the deposit is still entirely extracellular. Hematoxylin and eosin stain × 160.

two had coronary arteriosclerosis, hypertension and calcareous aortic stenosis. In two patients with cardiomegaly, both with 2 plus amyloid, no other contributory cardiac abnormality was evident. If one excludes patients with minimal amyloid deposit and with minor degrees of cardiomegaly, there were seven (of the nineteen) cases in which it appeared that the amyloid might have contributed in part to cardiac enlargement.

If cardiac amyloidosis were a slowly progressive process one would anticipate an increasing deposit with increasing age. However, analysis according to age and severity (Table v) indicates that the variations in severity of amyloidosis were fairly constant in the different age groups. It would thus appear more likely that the deposit accumulated during an interval of less than a decade and reached its maximum in a given case. There was no evidence to indicate that resorption of the deposit occurred, although this would be difficult to establish. Such a phenomenon has been described in secondary amyloidosis [*19–21*].

The frequency with which amyloid deposits were encountered in other tissues and organs is summarized in Table vi. The areas most commonly affected were the pulmonary capillaries and the walls of blood vessels in the pancreas, ovary, uterus and adrenal. The prominence and frequency of extracardiac deposits tended to be greater in cases of maximal cardiac infiltration.

The necropsy protocols of all forty-two cases were also reviewed for pertinent data; i.e., the occurrence of chronic disease, inflammatory disorders, state of nutrition, and malignant neoplasm. (Table iv.) Neither chronic inflammatory and non-amyloid degenerative lesions nor malignant neoplasms were of unusual frequency or extent. The degree of arteriosclerosis, generalized and coronary, encountered was similar to that observed in other patients in this age range. There were no correlations either with coronary occlusive disease or with foci of myocardial necrosis or fibrosis. The relatively poor state of general nutrition, as manifested by the general appearance of the subject, and the hepatic weight were of the anticipated order in a group of aged hospital patients [*22*]. There were neither clinical nor pathologic indications of an unusual incidence of hypovitaminosis, hypoproteinemia or anemia.

TABLE II

SEX AND RACE DISTRIBUTION OF CARDIAC AMYLOIDOSIS

Sex	No. Autopsies	Cases of Amyloidosis	Per cent Incidence
White			
Male	1,071	18	1.6
Female	592	10	1.8
Total	1,663	28	1.7
Negro			
Male	399	7	1.7
Female	249	7	2.8
Total	648	14	2.2
Total male autopsies		1,470	
Incidence in males		25 (1.7%)	
Total female autopsies		841	
Incidence in females		17 (2.0%)	

TABLE III

RELATION OF CARDIAC AMYLOIDOSIS TO HEART WEIGHT

Amount of Amyloid	No. of Cases	Average Weight (gm.)	Weight (gm. to nearest 5 gm.)				
			Less than 300	300–345	350–395	400 or more	> 373
± (less than 5%)	8	378	0	5	1	2	3
1+ (5–10%)	11	363	3	3	2	3	5
2+ (10–25%)	11	394	1	3	2	5	5
3+ (25–50%)	7	377	3	1	1	2	3
4+ (50% or more)	5*	450	0	1	1	3	3
Control subjects	42	373	12	6	8	16	21

* Four of five known to be hypertensive; one with no history available

TABLE IV

PATHOLOGIC FINDINGS IN FORTY-TWO PATIENTS WITH AMYLOIDOSIS

	Severe (12)	Moderate (30)
Nutrition		
Emaciated	4	5
Poor	1	8
Normal	5	16
Obese	2	1
Respiratory disease		
Emphysema	8	20
Non-specific chronic inflammation	9	5
Pneumoconiosis	1	1
Congestion and edema	8	16
Tuberculosis	0	2 (mild or inactive)
Cardiovascular		
Generalized arteriosclerosis		
Mild	0	3
Moderate	4	10
Severe	8	17
Coronary arteriosclerosis		
Mild	0	3
Moderate	3	13
Severe	9	14
Acute myocardial infarction	1	2
Myocardial fibrosis	5	8
Congestive cardiac failure related to amyloidosis	8	3
Hepatic Disease		
Weight of liver		
Normal	3	15
Low	2	5
Increased	6	6
Average	1,310*	1,200†
Maximum	1,800*	1,800†
Minimum	1,075	850
Congestion	8	7
Fatty change	2	4
Cirrhosis	0	3
Hepatoma	0	2
Metastatic neoplasm	1	2
Malignant neoplasms		
Localized	1	4
Widespread	1	6

* Excluding one patient in whom weight was not recorded.
† Excluding four patients with massive neoplastic replacement.

TABLE V

RELATIONSHIP OF AGE TO AMOUNT OF AMYLOID

Age (yr.)	No. of Cases	Average Amount (1 to 4 +)	± and 1 +	2 +	3 +	4 +
60–69	1	4	0	0	0	1
70–79	12	1.6	5	5	1	1
80–89	21	1.6	12	2	4	3
90–99	8	1.8	2	4	2	0

TABLE VIA

LOCALIZATION OF AMYLOID IN FORTY-TWO CASES OF CARDIAC AMYLOIDOSIS

Organ	No. Examined Microscopically	No. in Which Amyloid was Present	Major Deposits Present
Aorta	38	1	
Major blood vessels	9	5	1
Larynx	0		
Lung	41	23	2
Tongue	1	0	
Esophagus	12	1	0
Stomach	13	0	
Intestine	25	2	0
Liver	39	1	0
Gallbladder and/or bile ducts	12	1	0
Pancreas	33	7	0
Kidney	42	5	1
Ureter	3	0	
Urinary bladder	13	2	0
Uterus	9	3	0
Ovary	6	3	0
Prostate	19	1	0
Testis	6	0	
Pituitary	11	0	
Thyroid	9	0	
Parathyroid	9	0	
Adrenal	38	4	0
Bone	31	0	
Spleen	39	1	0
Lymph node	11	0	
Central nervous system	17	0	
Skin	1	0	
Adipose tissue	42	2	1

Efforts were made to determine whether there were any common underlying clinical or laboratory features in the forty-two patients with cardiac amyloidosis. In view of the fact that clinical manifestations may be more pronounced in advanced stages of a disease, the patients were divided into two groups, one composed of cases of severe amyloidosis, (3 plus and 4 plus) and the other consisting of examples of moderate or slight deposit (∓ to 2 plus). (Table VII.)

Obviously, conventional clinical diagnostic procedures did not appear to aid in the detection of this disorder; the diagnosis of amyloidosis had been entertained antemortem in none of the patients. For this reason, neither the Congo red test nor gingival biopsy had been attempted. Electrocardiograms available in twenty-seven cases manifested low voltage in only two. Serum protein determinations showed no constant pattern, and electrophoretic studies had not been carried out. There was no correlation between treatment administered (antibiotic agents, steroid drugs, medication for cardiac disorders) and the occurrence of amyloidosis.

TABLE VIII
LOCALIZATION OF AMYLOID CORRELATED WITH QUANTITY IN HEART

Amyloid in Heart	Cases	Amyloid Present Elsewhere	Three or More Other Organs Involved
±	8	2	1
1+	11	5	1
2+	11	9	3
3+	7	6	4
4+	5	5	3
Total	42	27	12

TABLE VII
CLINICAL AND LABORATORY FINDINGS IN FORTY-TWO CASES OF AMYLOIDOSIS*

	Severe (12)	Moderate (30)
Duration of last admission		
24 hours	3	4
1–3 days	2	3
3–14 days	4	17
14 days or more	3	6
Blood pressure		
Elevated	5/11†	8/28‡
Lowered	1/11	2/28
White count		
Elevated	6/11§	25/28§
Lymphocytosis	0/7	1/17
Hemoglobin		
Average (gm. %)	13.2	12.8
<10	1/11	1/28
>12	8/11	18/28
Albuminuria	5/11	11/25
Azotemia (blood urea nitrogen >30)	6/9	13/23
Serum proteins (total <5 gm. %)	1/3	2/8
Electrocardiograms		
Low voltage	1/8	1/19
Non-specific abnormalities	6/8	15/19
Normal	1/8	3/19
Roentgenographic evidence of cardiomegaly	4/6	8/18
Cause of death		
Acute myocardial infarction	1	2
Cardiac failure from amyloid	4	0
Sudden death (?amyloid)	1	0
Cardiac failure, in part the result of amyloidosis	4	3
Others	2	25

* Where fractions are given, the denominator indicates the total number of cases examined, the numerator, the total number in which the finding was encountered.
† Excluding one subject in shock during entire hospital stay.
‡ Excluding two subjects in shock during entire hospital stay.
§ All with terminal infection.

Thus there appeared to be no specific clinical features characterizing this disorder.

One can only concur with Josselson et al. [*12*] who stated that the condition should be suspected "in the presence of congestive cardiac failure in an elderly patient, unaffected by hypertension, valvular, or coronary arterial disease, or other conditions known to be associated with cardiac failure." However, in our own experience cardiac failure attributable to amyloidosis occurred with significant frequency (in eight of twelve patients) only in those patients with extensive deposition; it was relatively uncommon in association with the milder lesions (in three of thirty patients). Moreover, the lesion quite frequently was accompanied by other forms of cardiac disease common in aged persons.

COMMENTS

The stains commonly employed for demonstrating amyloid in tissues, crystal violet and Congo red, demonstrate all varieties of amyloid equally well with the exception of that seen in association with multiple myeloma [*23*]. Therefore, careful anatomic study is required in each instance of cardiac amyloidosis in order to exclude varieties of amyloidosis other than the senile type. In a group of thirty cases of secondary amyloidosis Dahlin [*24*] observed cardiac involvement in 43 per cent. This incidence is higher than that reported in other series; the author indicated that the incidence was considerably higher than would have been recognized had not microscopic sections of the heart been stained with methyl violet. In all instances, the lesions appeared as minute perivascular deposits. Secondary amyloidosis occurs in all age groups, although the peak of incidence varies with the nature of the hospital reporting. Jacobi and Grayzel [*25*] stated that the highest incidence was in the first three decades of life. Chronic inflammatory disease, such as tuberculosis, osteomyelitis or bronchiectasis, invariably precedes the development of this form of amyloidosis.

Involvement of the heart in patients with generalized primary amyloidosis has been recorded often [*26–42*]. Eisen [*37*] emphasized the occurrence of the condition in middle aged or elderly persons and its tendency to appear in muscle of all varieties. He reported that the heart, tongue, musculature of the alimentary tract, skeletal muscles, and the media of small arteries everywhere were most conspicuously affected. These sites of predilectivity had also been observed by Lubarsch [*27*]. Dahlin [*43*] pointed out that the organs most severely affected in secondary amyloidosis may likewise be involved by the primary variety. He indicated that death in generalized primary amyloidosis occurred most commonly in the sixth decade.

Recently, it has been reported that the heart may also be affected in familial primary amyloidosis [*44–47*]. In this condition the onset of clinical manifestations is insidious, most frequently commencing in the third or fourth decades, and neurologic, cardiovascular, alimentary or endocrine disturbances attributable to widespread amyloid infiltration may develop. Death is usually the result of cachexia, intercurrent infection or cardiovascular failure. Electrophoretic analysis of serum proteins in subjects with this form of amyloidosis [*47*] revealed an atypical peak, migrating between the β and α-2 globulin zones. In addition, an elevation of serum lipoproteins was demonstrable by ultracentrifugation. It was possible by use of these two procedures to discover obscure examples of this disorder in which clinical manifestations were not apparent. It appears that the serum abnormality may represent the only evidence of the condition, although clinical manifestations attributable to amyloidosis may appear ultimately.

In multiple myeloma Lichtenstein and Jaffe indicated that the incidence of amyloidosis was approximately 10 per cent [*48*]. Bayrd and Bennett [*49*] found the incidence to be 15 per cent. The amyloid of myeloma is commonly deposited in unusual sites, i.e., bone, joint capsule, muscle, skin, subcutaneous tissue, mucous membrane, tongue, heart, lung, intestine and genitourinary tract [*48,49*]. In necropsy examinations of three patients with multiple myeloma, Bayrd and Bennett [*49*] found amyloid deposits in the heart as well as in other locations. A similarity in distribution of amyloid deposition in myeloma and that of primary systemic amyloidosis has long been appreciated [*48,49*]. It is of interest that Bayrd and Bennett occasionally observed amyloid substance within the myeloma cells. Since the plasma cell is not known to be phagocytic, this location was thought to indicate the site of origin of amyloid. Dahlin and Dockerty [*50*] likewise observed deposition of amyloid in or in close proximity to myeloma cells, and we, too, have had this experience [*23*].

The age of the patients affected and the characteristic distribution of the deposit are the features which distinguish the senile cardiac variety from other forms. In the forty-two cases serving as the basis for this report, amyloid was restricted largely to the heart and the vascular system. Myocardial deposits were interstitial rather than perivascular in location. In many instances minor vascular and perivascular deposits were encountered in other viscera, notably the lung and pancreas. (Table VIA.) In fact, minute deposits were noted in the pulmonary capillaries in more than half the cases. There was also a high frequency of occurrence in small blood vessels of the ovary and the uterus, and in the islets of Langerhans of the pancreas. In one case there was somewhat more involvement of the kidney, adrenal and adipose tissue than of the heart. The difference in distribution and localization of the extracardiac deposits from those encountered in secondary amyloidosis is striking. Spleen, kidney, adrenal parenchyma and liver were uncommonly involved. There was a good correlation between the extent of extracardiac deposition and the severity of the cardiac replacement. Although there were exceptions, generally speaking the greater the quantity of amyloid found in the heart, the more likely was significant infiltration in other viscera. (Table VIB.)

There appeared to be no single feature or combination of features that served to establish the clinical diagnosis of cardiac amyloidosis. This is probably responsible for the failure to recognize the existence of the lesion in any cases in this series prior to death. Indeed, a perusal of the clinical findings indicates that in most instances cardiac amyloidosis, of itself, produces no symptoms, particularly when there are only minor degrees of deposition. Only three of thirty patients in the group with minimal deposit exhibited evidence of cardiac disorder which might conceivably have been attributable to the amyloidosis. On the other hand, in eight of twelve patients with marked deposition cardiac failure may very well have been entirely or partially due to amyloidosis. (Tables IV and VII.) The infrequency with which electrocardiographic alterations were encountered (only two of twenty-seven tracings showed low voltage) is somewhat surprising, in view of the alleged specificity of this finding. Jones and Frazier [*13*] emphasized the importance of the presence of low voltage in the electrocardiogram as a hint during life of the existence of cardiac amyloidosis. However, in Hüsselmann's series [*16*] low voltage was uncommonly encountered. Indeed, Wessler and Freedberg [*51*] found that cardiac amyloidosis may be associated with a wide variety of changing electrocardiographic patterns. They pointed out that the electrocardiograms in cases of cardiac amy-

loidosis may simulate those in cases of myocardial infarctions.

Routine serum protein studies appeared to offer no substantial aid in the diagnosis of this condition. Unfortunately, no electrophoretic studies were available. Hüsselmann [*16*] performed electrophoretic studies on serum obtained at necropsy from fourteen patients with senile cardiac amyloidosis. Most commonly he observed lowered or normal total proteins and albumin, accompanied frequently by moderate increases in the α-2 and gamma globulin fractions. In some instances the β-globulin was also increased. He indicated that the pattern may resemble that seen in secondary amyloidosis in man and in experimentally induced amyloidosis in animals, but was not characteristic since it may also occur under a wide variety of other circumstances.

Numerous substances administered to experimental animals have produced amyloidosis: casein [*21,52,54-57*]; nutrose [*19,52,58*]; colloidal sulfur [*52*]; colloidal selenium [*52*]; colloidal gold [*60*]; serum [*58*]; vaccines [*59*]; necrosin [*60*]; and homo tissue transplants [*52*]. There is no evidence to suggest that similar agents contributed to the development of amyloidosis in our forty-two patients. Nor was there any indication (Tables IV and VII) that the nutritional state had any causal relationship. However, it has been observed experimentally that malnutrition or avitaminosis [*21,55,57,61,62*], or the administration of hormones [*54,55*], while not directly causative, may accelerate the formation of amyloid. Mulligan [*63*] considered malnutrition an important factor in influencing the development of senile cardiac amyloidosis but our observations do not support this concept.

The chemical composition of human and experimental amyloid deposits has been studied by means of many technics. The presence of acid mucopolysaccharide has been verified by both chemical [*64-66*] and histochemical [*23,67*] methods. Proteins, including globulins, have been demonstrated, utilizing fluorescent antibodies [*68,69*], chemical analysis [*70,71*] and electrophoresis [*65,66*]. Both in experimentally induced amyloidosis and in human subjects with secondary amyloidosis alterations in the serum proteins have been described, usually elevation of various globulin fractions [*52-54,57, 72,73*]. However, similar patterns noted by Hüsselmann [*16*] in patients with senile cardiac amyloidosis were inconstantly present and not specific for this condition.

The frequent demonstration of abnormalities in serum proteins associated with amyloidosis has led many observers [*64,65,68,74*] to suggest that amyloid deposits represent precipitates formed in tissues as a result of a reaction between antigens and antibodies. Calkins, Cohen and Gitlin [*75*] have recently reported data indicating that this concept is not valid. Teilum [*76*], Letterer [*57*], Smetana [*77*], and Grayzel and co-workers [*21*] all observed an association of amyloid production in the experimental animal with proliferation of mesenchymal cells; the last group indicated that the deposit first appeared within reticuloendothelial cells. In the present study amyloid never appeared within cells or in proximity to proliferating histiocytes or plasma cells. Moreover, abnormalities in serum proteins were generally lacking, and in no case was there present any condition known to be associated with a protracted immune response. These observations indicate that none of the hypotheses suggested offer an adequate explanation of the pathogenesis of senile cardiac amyloidosis.

SUMMARY AND CONCLUSIONS

Senile cardiac amyloidosis represents a distinct variety of amyloidosis, which occurs in aged persons of both sexes, and in white and Negro subjects with equal frequency, and is restricted largely to the cardiovascular system; the incidence increases with increasing age but deposition does not appear to be cumulative. Cardiomegaly is not a prominent feature of the disorder but cardiac failure may occur when amyloid is deposited in large quantities.

The study revealed neither characteristic symptoms nor specific diagnostic methods by means of which a definite clinical diagnosis may be established. The high incidence of this disease in aged persons should suggest the diagnosis in all elderly patients with cardiac failure not explainable on the basis of other lesions.

A review of the pathologic findings noted at necropsy failed to reveal any specific etiologic factors. An apparent increase in incidence in recent years in our material was restricted to subjects in the tenth decade.

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University of Cincinnati performed the statistical analyses.

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The Effect of a New Carbonic Anhydrase Inhibitor (Dichlorphenamide) in Respiratory Insufficiency*

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ACUTE respiratory insufficiency with hypoxia and respiratory acidosis can usually be alleviated by intensive therapy directed at reducing the work of breathing and increasing alveolar ventilation. Such therapy includes antibiotics, bronchodilators, detergents, oxygen, the management of heart failure and mechanical respiratory assistance. Chronic carbon dioxide retention, however, is relatively refractory to these measures. There is, therefore, a continual search for new aids in the management of this condition.

Several reports have appeared dealing with the efficacy of acetazoleamide in respiratory acidosis [*1–5*]. While results were equivocal in some patients, definite benefit was observed when a significant diuresis was produced. Even when beneficial, however, the development of hyperchloremic acidosis during prolonged administration of the drug limited its effectiveness.

Recently dichlorphenamide (daranide, Merck Sharpe and Dohme), which has a capacity to inhibit carbonic anhydrase estimated to be thirty times that of acetazoleamide, has been developed [*6*]. It presumably differs from the latter agent in that it is capable of producing a chloruresis so that metabolic acidosis is less likely to occur. This paper reports the beneficial effects of dichlorphenamide therapy in fifteen patients with chronic respiratory insufficiency.

METHODS AND MATERIALS

Patients admitted to the hospital because of respiratory insufficiency were placed on a regimen which, according to the clinical findings, included some or all of the following measures: antibiotics, bronchodilators, digitalis, diuretics, oxygen and intermittent positive pressure breathing. If hypercapnia persisted after one to two weeks of intensive therapy, 200 mg. of dichlorphenamide/day was added to the regimen and continued over periods ranging from two to thirty weeks. Thirteen such patients were studied, eleven with emphysema, one with thoracoplasty for tuberculosis, and one with kyphoscoliosis. In addition, two patients with hypoxia and minimal hypercapnia due to pulmonary fibrosis were placed on this regimen. The diagnosis, physical characteristics and ventilatory function of all the patients before the administration of dichlorphenamide is shown in Table 1. Clinical evidence of marked functional impairment was associated with hypoxia and hypercapnia in each case.

Simultaneous samples of expired air and arterial blood were collected on repeated occasions in nine patients, while arterial blood alone was analyzed in the remaining six. In each case collections were made after a fifteen- to twenty-minute period of quiet recumbency. Expired gas was collected in a Tissot spirometer and was analyzed for oxygen and carbon dioxide concentration by the micro-Scholander technic [*7*]. Arterial oxygen and carbon dioxide tensions were measured by the bubble equilibration method of Riley et al. [*8*], as modified by Brinkman et al. [*9*], while arterial oxygen and carbon dioxide contents were determined manometrically [*10*].

From these estimations and the spirometer record, it was possible to calculate minute ventilation, tidal volume, respiratory frequency, physiological dead space, alveolar ventilation, oxygen consumption, carbon dioxide elimination and "ideal" alveolar oxygen tension [*11*].

RESULTS

All patients but one (A. S.) claimed definite symptomatic improvement with less dyspnea,

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TABLE I

PHYSICAL CHARACTERISTICS AND PULMONARY FUNCTION OF PATIENTS STUDIED

Patient	Diagnosis	Age (yr.)	Sex	Body Surface Area (M^2)	Vital Capacity (ml.)		Maximum Breathing Capacity (L./min.)		Expiratory Maximum Mid-flow (L./sec.)	Alveolar N_2 after 7 Min. Oxygen (%)	Arterial	
					Observed	% Predicted	Observed	% Predicted			pO_2 (mm. Hg)	pCO_2 (mm. Hg)
F. N.	Emphysema	61	M	1.52	2,650	70	32	33	0.40	14.6	36	64
G. W.	Emphysema	67	M	1.69	2,440	73	38	45	0.38	8.3	36	68
F. R.	Emphysema	53	M	1.83	2,920	74	31	29	0.27	18.0	46	66
L. F.	Emphysema	67	M	1.51	.....	...	....	....	.....	.....	53	64
M. P.	Emphysema	45	M	1.70	1,185	29	20	18	0.45	12.3	41	64
W. K.	Emphysema	66	M	1.83	1,840	60	11	14	0.20	6.9	31	82
G. S.	Emphysema	71	M	1.46	.....	...	....	....	.....	7.4	44	79
R. S.	Emphysema	58	M	1.92	2,750	69	33	32	0.38	19.0	55	67
A. M.	Emphysema	60	F	1.58	.....	...	....	....	.....	.....	31	73
H. L.	Emphysema	56	M	1.72	2,590	69	35	35	0.22	10.2	69	53
S. M.	Emphysema	68	M	1.79	.....	...	....	....	.....	2.5	64	62
M. T.	Tuberculin bacillus thoracoplasty	42	F	1.65	625	22	17	20	0.96	2.9	36	80
A. S.	Kyphoscoliosis	38	F	1.31	640	22	22	24	0.73	1.8	27	65
J. H.	Diffuse fibrosis	56	M	1.79	2,400	68	108	114	1.26	1.7	57	50
F. I.	Silicosis	60	M	1.88	3,810	95	105	101	2.63	0.8	76	51

increased effort tolerance and a general sense of well-being while receiving dichlorphenamide. Two patients experienced mild nausea which was relieved by administering the drug with meals. In one patient severe headache developed which disappeared when placebo therapy was substituted.

A typical example of the effect of dichlorphenamide on arterial blood gas tensions is illustrated in Figure 1. One patient (W. K.), with known carbon dioxide retention of at least four years' duration, was severely hypoxic and hypercapnic despite vigorous, intensive treatment, including intermittent positive pressure breathing. The administration of dichlorphenamide resulted in marked clinical improvement which was associated with a fall in carbon dioxide tension and an increase in oxygen tension. When administration of the drug was withheld obvious clinical deterioration occurred and hypoxia and hypercapnia were aggravated. Reinstitution of dichlorphenamide therapy was once more associated with marked clinical improvement and improved arterial gas tensions which persisted for the ten weeks that this patient was available for study. In another patient (F. N.), substitution of placebo therapy for dichlorphenamide was associated with clinical deterioration and aggravation of hypoxia and hypercapnia.

Table II presents the mean and range of arterial gas tensions obtained before and during the administration of dichlorphenamide in all patients studied. Two to five studies before and four to ten studies during the administration of dichlorphenamide were performed in each patient at intervals of two to ten days. During dichlorphenamide administration there was a marked reduction in hypercapnia in all patients but one (A. S.), the mean decrease being 10.9 mm. Hg. In addition there was a consistent rise in arterial oxygen tensions, the mean increase being 16.3 mm. Hg. It should be pointed out that the change in mean arterial gas tensions is

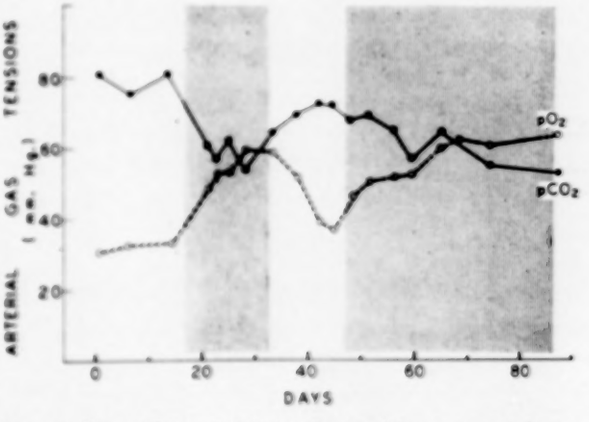

FIG. 1. The effect of dichlorphenamide on arterial gas tensions in patient W. K. The cross-hatched areas represent intervals during which 200 mg. dichlorphenamide/day was administered.

TABLE II

THE EFFECT OF DICHLORPHENAMIDE ON ARTERIAL GAS TENSIONS

Patient	Arterial pCO_2 (mm. Hg)			Duration of Treatment (wk.)	Arterial pO_2 (mm. Hg)		
	Pre-treatment	Treatment	Change in Mean		Pre-treatment	Treatment	Change in Mean
F. N.	50.4 38.0–64.0	41.0 37.0–48.0	−9.4	30.0	56.8 36.0–69.0	73.3 68.0–83.0	+16.5
G. W.	58.0 53.0–68.0	48.5 45.0–51.0	−9.5	13.0	51.0 36.0–59.0	66.6 63.0–68.0	+15.6
F. R.	63.0 60.0–66.0	53.0 44.0–61.0	−10.0	12.0	40.6 35.0–46.0	61.8 54.0–70.0	+21.2
L. Z.	63.5 63.0–64.0	55.2 51.0–61.0	−8.3	11.0	51.5 50.0–53.0	59.0 54.0–66.0	+7.5
M. P.	59.8 57.0–64.0	45.6 41.0–48.0	−14.2	8.0	48.5 42.0–55.0	67.6 66.0–71.0	+19.1
W. K.	75.3 69.0–82.0	61.0 54.0–69.0	−14.3	8.0	37.5 31.0–52.0	56.3 51.0–65.0	+18.8
D. N.	77.5 76.0–79.0	55.0 48.0–56.0	−22.5	4.5	40.0 38.0–42.0	64.0 42.0–75.0	+24.0
R. N.	60.0 55.0–67.0	54.3 51.0–57.0	−5.7	4.0	58.0 55.0–61.0	71.3 66.0–80.0	+13.3
A. M.	74.0 73.0–75.0	54.5 50.0–59.0	−19.5	2.0	33.0 31.0–35.0	52.0 51.0–53.0	+19.0
H. L.	51.5 50.0–53.0	44.5 41.0–48.0	−7.0	2.0	68.0 67.0–69.0	69.5 68.0–71.0	+1.5
S. M.	59.0 56.0–62.0	41.3 39.0–45.0	−17.7	1.5	64.5 64.0–65.0	89.2 80.0–93.0	+24.7
M. T.	75.0 70.0–80.0	56.5 50.0–64.0	−18.5	12.0	42.0 36.0–48.0	63.0 55.0–69.0	+21.0
A. S.	66.6 65.0–68.0	69.0 66.0–72.0	+2.4	3.0	32.0 27.0–35.0	48.0 43.0–58.0	+16.0
J. H.	48.5 47.0–50.0	42.5 40.0–45.0	−6.0	7.0	57.5 57.0–58.0	66.0 62.0–70.0	+8.5
F. J.	48.5 46.0–51.0	44.5 40.0–49.0	−4.0	2.0	69.0 62.0–76.0	86.5 84.0–89.0	+17.5

an underestimate of the beneficial clinical effect of the drug, since progressive improvement was observed in almost all cases.

The effect of dichlorphenamide on arterial carbon dioxide content and pH is shown in Table III. The arterial carbon dioxide content was markedly reduced in all patients during treatment with the drug with a mean decrease of 6.25 mM./L. The calculated arterial pH tended to decrease particularly during the initial phase of the administration of dichlorphenamide and then tended to return toward the original value. The mean decrease in arterial pH was 0.047 units.

The effect of dichlorphenamide on "ideal" alveolar oxygen tension and calculated A-a gradient for oxygen is shown in Table IV. It is to be noted that the alveolar oxygen tension rose in seven of nine patients studied. Despite a concomitant rise in arterial pO_2, the A-a oxygen tension gradient was greater during dichlorphenamide therapy in five of these subjects. In two, the arterial oxygen tension rose in the absence of a rise in alveolar oxygen tension, so that the A-a oxygen tension gradient fell during dichlorphenamide administration.

Table IV also presents the effect of dichlorphenamide on alveolar ventilation in nine patients. It can be seen that the alveolar ventilation was increased in the seven patients in whom a rise in alveolar oxygen tension was also noted. The mean increase in alveolar ventilation was 0.67 L./minute. This was associated with a mean increase in minute ventilation of 0.60 L./

TABLE III

THE EFFECT OF DICHLORPHENAMIDE ON ACID-BASE BALANCE

Patient	pH			Carbon Dioxide Content (mM./L.)		
	Pre-treatment	Treatment	Change in Mean	Pre-treatment	Treatment	Change in Mean
F. N.	7.37	7.28	−0.09	23.6	17.1	−6.5
	7.29–7.40	7.23–7.34		19.0–29.9	15.2–19.4	
G. W.	7.32	7.29	−0.03	25.6	19.7	−5.9
	7.22–7.40	7.22–7.34		24.0–28.7	18.0–20.4	
F. R.	7.35	7.29	−0.06	27.9	20.3	−7.6
	7.29–7.36	7.23–7.36		26.4–29.2	19.4–21.8	
L. Z.	7.28	7.27	−0.01	25.5	21.8	−3.7
	7.27–7.35	7.24–7.32		25.4–25.6	20.2–23.4	
M. P.	7.33	7.29	−0.04	26.6	18.9	−7.7
	7.29–7.36	7.27–7.33		24.6–30.0	16.7–21.0	
W. K.	7.28	7.28	0.0	30.2	24.8	−5.4
	7.26–7.29	7.19–7.35		26.8–32.5	21.5–28.9	
B. N.	7.29	7.29	0.0	31.3	22.8	−8.5
	7.28–7.30	7.23–7.34		30.9–31.7	21.8–25.2	
R. N.	7.34	7.26	−0.08	25.4	20.8	−4.6
	7.31–7.37	7.25–7.27		24.9–26.6	20.6–20.9	
A. M.	7.32	7.32	0.0	32.0	24.1	−7.9
	7.31–7.32	7.27–7.38		31.5–32.5	23.5–24.6	
H. L.	7.41	7.35	−0.06	26.5	20.4	−6.1
	7.39–7.42	7.34–7.36		26.1–26.8	19.5–21.2	
S. M.	7.32	7.37	+0.05	25.7	18.9	−6.8
	7.28–7.36	7.34–7.39		25.2–26.1	17.8–20.5	
M. T.	7.31	7.27	−0.04	34.1	24.5	−8.6
	7.27–7.35	7.26–7.28		32.8–33.4	22.1–25.8	
A. S.	7.35	7.29	−0.06	33.2	29.3	−3.9
	7.24–7.43	7.28–7.32		30.7–36.6	28.0–31.4	
J. H.	7.33	7.25	−0.08	20.6	16.0	−4.6
	7.31–7.34	7.25–7.26		20.4–20.7	15.1–16.8	
F. J.	7.33	7.22	−0.11	22.5	16.6	−5.9
	7.33	7.18–7.26		21.2–23.8	16.3–16.8	

minute, and, in most instances, with a slowing of respiratory rate and increase in tidal volume.

Since ventilation increased during dichlorphenamide therapy, a study was undertaken to assess the sensitivity of the medullary respiratory center by measuring the ventilatory response to inhaled carbon dioxide before and after administration of 200 mg. dichlorphenamide daily for one week in three normal and three emphysematous subjects. The minute ventilation was measured, after a steady state had been reached, while breathing ambient air and from one to three gas mixtures with increased carbon dioxide concentrations. In the patients with emphysema, the arterial pCO_2 was measured, while in the normal subjects, end tidal pCO_2, used as an index of arterial pCO_2, was measured by means of a rapid infra-red carbon dioxide analyzer.

The effect of dichlorphenamide on the ventilatory response to inhaled carbon dioxide in the three normal and three abnormal subjects is shown in Figure 2. It can be seen that in most cases the ventilation was higher and the carbon dioxide tension lower at rest while dichlorphenamide was being administered. This was associated with an increase in tidal volume in all cases. It should be noted that while the response lines relating pCO_2 to ventilation were shifted to the left in each case, the slopes of the lines did not differ greatly, indicating that the ventilatory response to a given change in arterial carbon dioxide tension was unaltered during the administration of dichlorphenamide.

TABLE IV

THE EFFECT OF DICHLORPHENAMIDE ON ALVEOLAR VENTILATION, ALVEOLAR PO_2 AND A-a OXYGEN TENSION GRADIENT

Patient	Mean Alveolar Ventilation (L./min.)		Mean Alveolar pO_2 (mm. Hg)		Mean Alveoloarterial pO_2 Gradient (mm. Hg)	
	Pretreatment	Change with Treatment	Pretreatment	Change with Treatment	Pretreatment	Change with Treatment
F. R.	3.00	+2.29	53.5	+31.5	10.0	+13.0
M. P.	3.78	+1.09	71.5	+23.5	17.5	+10.5
R. N.	3.46	+1.15	69	+10.5	12.0	+0.5
H. L.	3.66	+0.67	78	+8.5	10.0	+7.0
S. M.	3.53	+0.40	81	+13.0	9.0	−3.0
M. T.	2.63	+0.96	48.5	+26.5	6.5	+3.5
A. S.	2.57	−0.33	62	−7.0	31.0	−18.0
J. H.	5.68	−0.59	94	−3.0	39.5	−18.5
F. J.	3.38	+0.41	82	+9.0	6.0	−1.0

The oxygen consumption and carbon dioxide elimination showed no consistent trends during dichlorphenamide administration. Early transient changes, however, may have been missed.

A diuresis, as indicated by significant weight loss, was noted in two patients (A. M. and S. M.) during dichlorphenamide therapy. The weights of the other patients, however, did not change from their initial weights by more than 3 pounds.

The effect of dichlorphenamide on the urinary output of water and electrolyte was studied in three patients. Two of these (M. T. and F. R.) received standard ward diets while one (M. P.) ingested a diet of fixed electrolyte content in

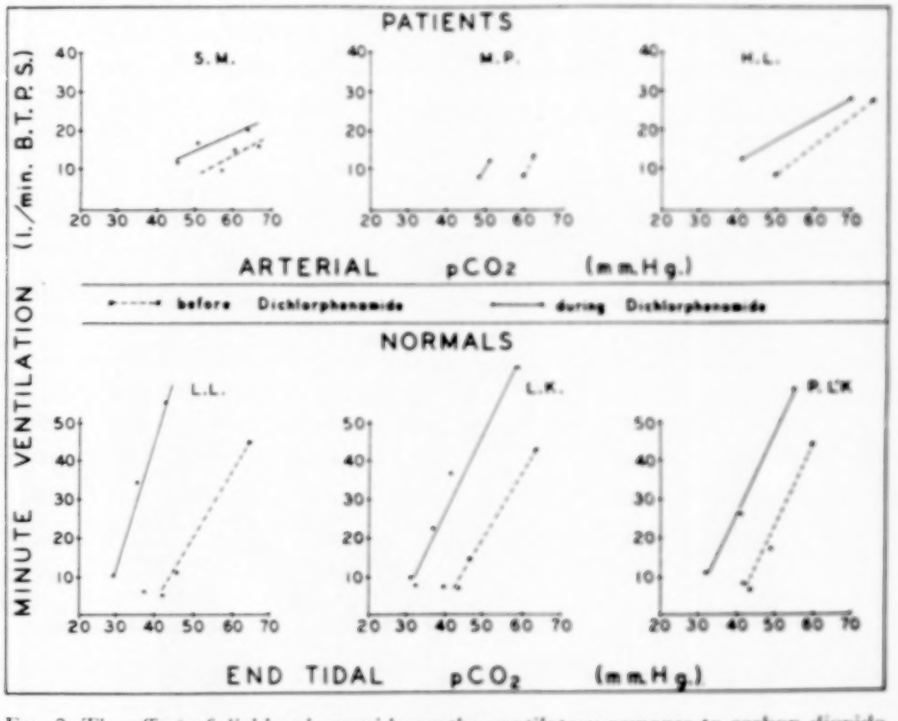

FIG. 2. The effect of dichlorphenamide on the ventilatory response to carbon dioxide in three normal and three emphysematous subjects.

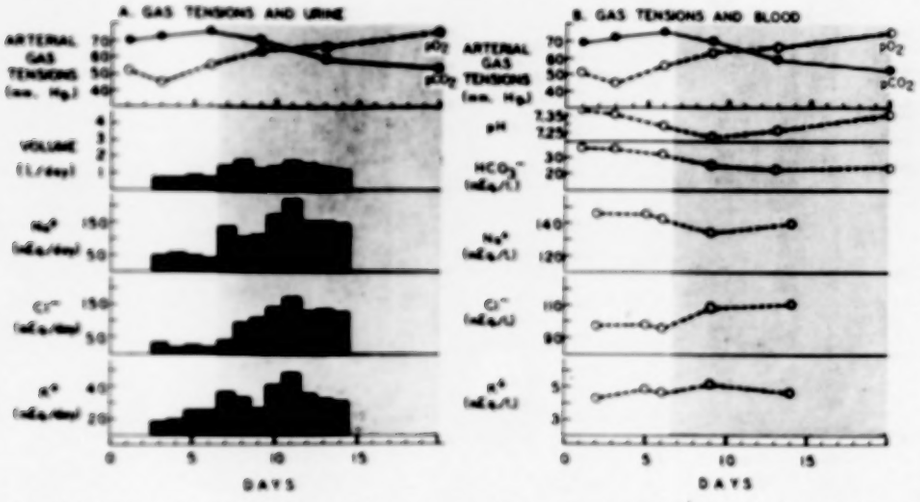

FIG. 3. The effect of dichlorphenamide on arterial blood gas tensions and blood and urinary electrolytes in patient F. R. while on a standard ward diet. The stippled area represents the interval during which 200 mg. dichlorphenamide/day was administered. Changes in arterial gas tensions are plotted with concomitant urinary changes in (A) where electrolyte output is plotted, and with concomitant blood changes in (B).

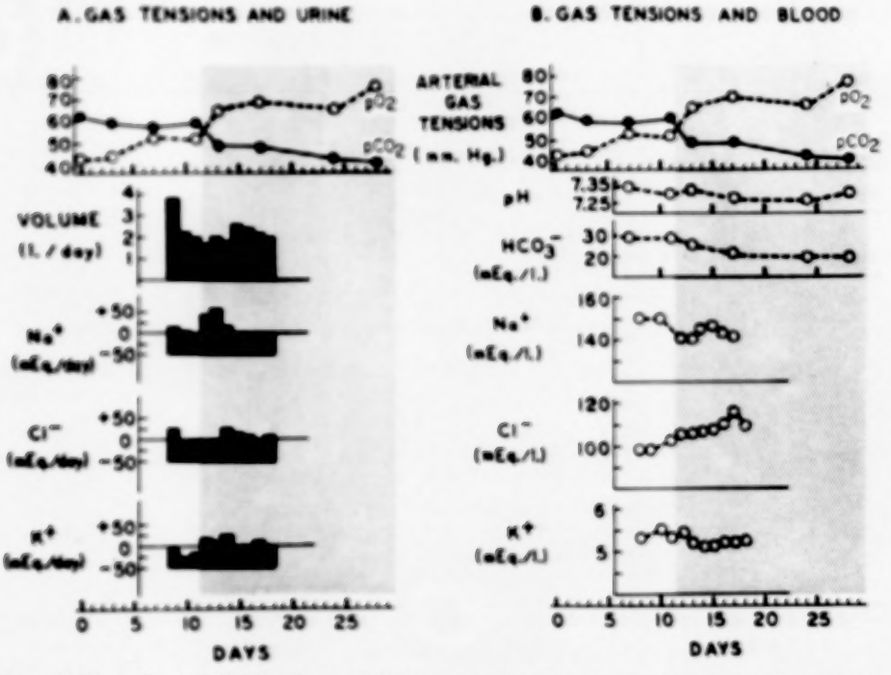

FIG. 4. The effect of dichlorphenamide on arterial gas tensions and urinary electrolytes in patient M. P. while on an intake of 1,100 mg. sodium/day. The stippled area represents the interval during which 200 mg. dichlorphenamide/day was administered. Changes in arterial gas tensions are plotted with concomitant urinary changes in (A) where electrolyte intake minus output is plotted, and concomitant blood changes in (B).

3 L. of fluid daily. Daily twenty-four-hour urine samples were frozen and subsequently analyzed for sodium, potassium and chloride by standard technics. Serum sodium, potassium and chloride determinations were made on venous blood.

Figure 3 illustrates the effect of dichlorphenamide on some constituents of urinary output and the serum electrolytes in one patient (F. R.) who ingested a standard ward diet. The changes in arterial gas tensions are plotted with concomitant changes in urinary constituents in Figure 3A and with serum electrolytes in Figure

3B. It can be seen that the administration of dichlorphenamide resulted in an increase in urinary output with an increase in sodium, potassium and chloride excretion. This was associated with a fall in arterial pH and bicarbonate, and serum sodium. Despite the chloruresis, however, the serum chloride rose. Results in the other patient on the standard diet were similar.

The changes in blood gas tensions, urinary constituents and serum electrolytes in a patient (M. P.) who was on a fixed dietary intake are shown in Figure 4. In this patient there was only an initial transient increase in sodium and potassium excretion followed by minimal chloruresis during the administration of dichlorphenamide. There was a transient minor increase in urine volume, the patient's weight remaining constant during the period of observation. In addition, the serum sodium concentration decreased concomitantly with a less evident decrease in serum potassium concentration during dichlorphenamide administration. Serum chloride concentration rose and arterial plasma bicarbonate concentration fell, the arterial pH falling initially and then slowly returning towards the control level.

COMMENTS

The data presented indicate that the administration of dichlorphenamide to patients with pulmonary insufficiency resulted in marked clinical improvement, a fall in arterial carbon dioxide tension and a rise in arterial oxygen tension.

The arterial carbon dioxide tension at any moment is directly related to the carbon dioxide production and inversely related to the rate of elimination of carbon dioxide by the lungs. The finding of a reduced arterial carbon dioxide tension during dichlorphenamide therapy could therefore be explained by either decreased carbon dioxide production by the tissues, increased alveolar ventilation, or both. Tenney and Tschetter [*12*] have demonstrated a decreased metabolic rate in rats chronically maintained on acetazoleamide while Mithoefer [*13*] has shown an initial decrease in carbon dioxide elimination which was due to an increase in body carbon dioxide stores in dogs following the administration of acetazoleamide. No changes in oxygen consumption or carbon dioxide elimination were observed during dichlorphenamide administration in the present study. However, minor changes in metabolism may have been obscured by changes in the clinical status of the patient.

On the other hand, alveolar ventilation increased in most patients and in the three normal subjects when dichlorphenamide was administered. All tended to breathe more deeply, and some more slowly, during the administration of dichlorphenamide.

It is of interest that this increase in ventilation was not associated with an increase in oxygen consumption since it has been demonstrated that the oxygen consumption increases considerably with increased ventilation in patients with emphysema [*14–16*]. However, the mean increase in ventilation was not marked and a change in oxygen consumption may have been missed.

The resting ventilation was increased and arterial pCO_2 decreased in both normal and abnormal subjects while receiving dichlorphenamide. This suggests that dichlorphenamide resulted in stimulation of the respiratory center with a consequent lowering of pCO_2. Similarly an increased alveolar ventilation has been observed in some patients during administration of acetazoleamide [*1–5,13*] while an altered response to carbon dioxide has not been demonstrated [*14,18*]. The unaltered slope of the "stimulus-response lines" during acetazoleamide and dichlorphenamide administration suggests that the response of the respiratory system to changes in arterial pCO_2 was not increased. On the other hand, it is possible that while arterial pCO_2 was lower during therapy, a carbon dioxide gradient may have been present between tissues and arterial blood. Thus, the carbon dioxide tension of the tissues, and the respiratory centers, could actually be higher than that prior to therapy due to the carbonic-anhydrase inhibiting effect of the drug. This might account for an increased ventilation at rest during dichlorphenamide therapy.

The increase in alveolar ventilation resulted in an elevated alveolar oxygen tension and an associated rise in arterial oxygen tension. The alveolar-arterial oxygen tension difference tended to increase in some patients, perhaps because of the increased effect of "venous admixture" on arterial pO_2 at higher alveolar oxygen tensions. The rise in arterial oxygen tension despite no change in alveolar oxygen tension in two patients (J. H. and A. S.) might perhaps be explained by an increase in pulmonary blood flow during dichlorphenamide therapy. However, the extent to which an increased pulmonary blood flow was responsible for the changes observed was not assessed.

A diuresis resulting in elimination of pulmonary congestion would lead to an improvement in arterial gas tensions. A slight diuretic effect was in fact noted in some patients. However, this was not demonstrated in many patients who had striking clinical improvement and alleviation of hypoxia and hypercapnia. Thus the beneficial effects of dichlorphenamide would not be correlated with a decrease in pulmonary congestion.

It is of interest to note that dichlorphenamide resulted in a marked chloruresis in the patients on a standard ward diet but not in the patient on a fixed sodium and chloride intake. Thus while a metabolic acidosis developed in the patient on a fixed sodium and chloride intake this was not so in the patient on a ward diet.

In addition, the data suggest that dichlorphenamide has two sites of action; a renal effect, accounting for the marked excretion of sodium and bicarbonate and producing a metabolic acidosis and an effect on other tissues, e.g., the respiratory center resulting in an increase in ventilation and lowering of pCO_2. The equivocal results reported with acetazoleamide might, therefore, be due to the fact that its effect is primarily on the kidney.

Whatever its mode of action, however, dichlorphenamide therapy has produced striking benefit in fourteen of fifteen patients with pulmonary insufficiency who were studied. This drug, therefore, would appear to be a valuable adjunct in the therapy of chronic respiratory insufficiency.

SUMMARY

The effect of a new carbonic anhydrase inhibitor, dichlorphenamide, has been studied in fifteen patients with respiratory insufficiency. All but one showed clinical improvement. In most cases marked improvement in arterial blood gas tension was associated with an increased alveolar ventilation. This improvement has been sustained during prolonged administration of the drug. Possible mechanisms of action of this drug have been investigated and discussed.

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The Effect of Sodium Loading and Depletion on Muscular Strength and Aldosterone Excretion in Familial Periodic Paralysis*

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FAMILIAL periodic paralysis is a disease of dominant inheritance characterized by recurrent attacks of flaccid skeletal muscle paralysis associated with absent deep tendon reflexes and inexcitability to direct electrical stimulation. Hypokalemia during attacks, although usual, is not universal and correlates imperfectly with the degree of weakness. Conn et al. [*1–3*] have reported an increased aldosterone excretion prior to attacks and a prophylactic effect of dietary sodium restriction. The present report represents an attempt to determine the effect of sodium depletion and loading on muscular strength, and the role of aldosterone in the pathogenesis of attacks in this disease.

CASE REPORTS

The principal subject of this investigation, conducted at the National Institutes of Health from January to June 1958, was a twenty-five year old white male federal prisoner who, from the age of four, had had intermittent muscular weakness affecting the trunk and extremities. During mild attacks he noted difficulty only in walking and climbing stairs. During severe attacks he was confined to bed and unable to lift his extremities or change his position. The affected muscles felt heavy but were not painful. Micturition and defecation never occurred during severe attacks. Cranial musculature was rarely affected and sensation and mental state were always normal. The attacks, which frequently began at night, were precipitated by rest, the ingestion of sugar or starches, and cold. They were relieved by exercise and the ingestion of potassium salts. Since their onset, the attacks had become steadily more frequent and more severe except for a partial remission for one year at the age of sixteen. At the time of our study, the patient awoke noticeably weak every morning despite 1 ounce of 25 per cent aqueous solution of potassium chloride taken orally three or four times daily. The patient had never been able to do push ups, chin himself, run fast or lift heavy weights, but this interval weakness had not been progressive. He denied having any gastrointestinal or renal symptoms and, except for joint pains and fever at the age of seven, had enjoyed good health.

Physical examination revealed an alert, well nourished young man with poor muscular development of the trunk and upper extremities. Between attacks he manifested mild symmetrical proximal muscular weakness and hypoactive deep tendon reflexes in all extremities. An apical presystolic murmur and conduction deafness in the left ear were the only additional interval physical findings. His blood pressure was normal. During severe attacks, the patient had almost complete quadriplegia with absent deep tendon reflexes and muscles inexcitable on direct stimulation. A 50 per cent reduction in vital capacity, bradycardia and a sinus arrhythmia frequently occurred. The only consistent alteration in serum electrolytes was hypokalemia, accompanied by the characteristic electrocardiographic changes. Attacks were precipitated by inactivity, especially following strenuous exercise; glucose, especially when administered with insulin; omission of potassium chloride; and less effectively by epinephrine or exposure to cold. Water loading had no effect. The patient never manifested myotonia by clinical testing or by electromyography.

Blood urea nitrogen, fasting blood sugar, plasma corticoids, serum protein-bound iodine, radioactive iodine uptake, roentgenograms of the skull, intravenous pyelography, urinalysis including examination for porphobilinogen and myoglobin during attacks, and twenty-four-hour urinary excretion of potassium, 17-hydroxycorticoids, and 17-ketosteroids were within normal limits. The oral glucose tolerance test showed a delayed rise, which is considered characteristic of periodic paralysis by MacGregor [*4*].

The patient's brother, a nineteen year old college

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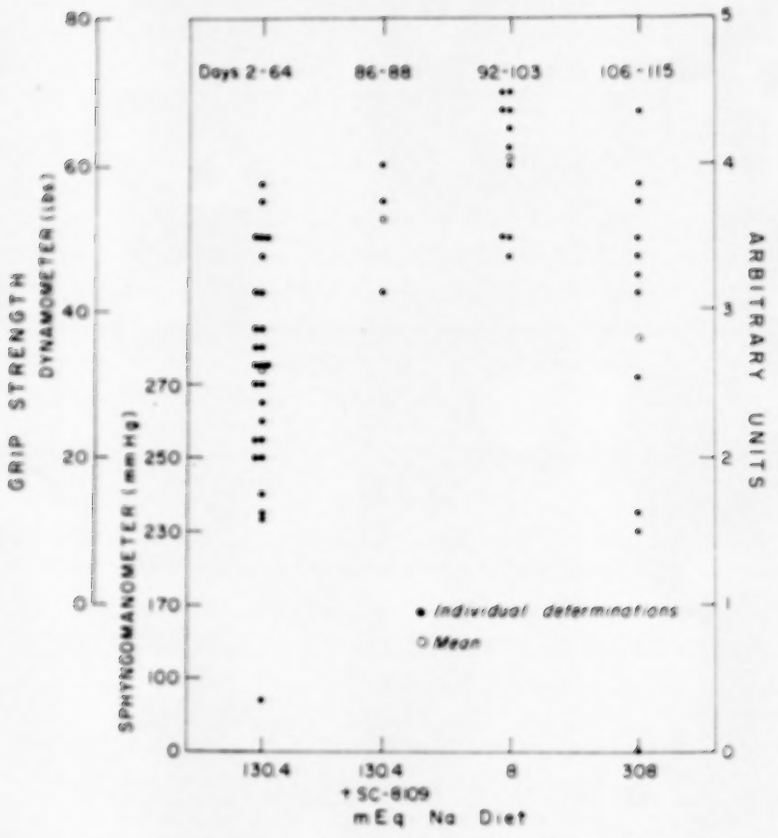


FIG. 1. Effect of different sodium intakes and of SC-8109 on grip strength tested between 8 and 9 A.M.

student, had had similar attacks since the age of fifteen and was studied at the National Institutes of Health in June 1958. Between attacks, he also evidenced slight symmetrical proximal muscle weakness and hyposactive deep tendon reflexes. His attacks resembled those of his brother in precipitating and ameliorating factors, but they were less frequent and less severe.

The patient's sister, a twenty-three year old housewife, also had had mild attacks of a similar nature since the age of fifteen. She had experienced an exacerbation during, and a remission following, a recent pregnancy.

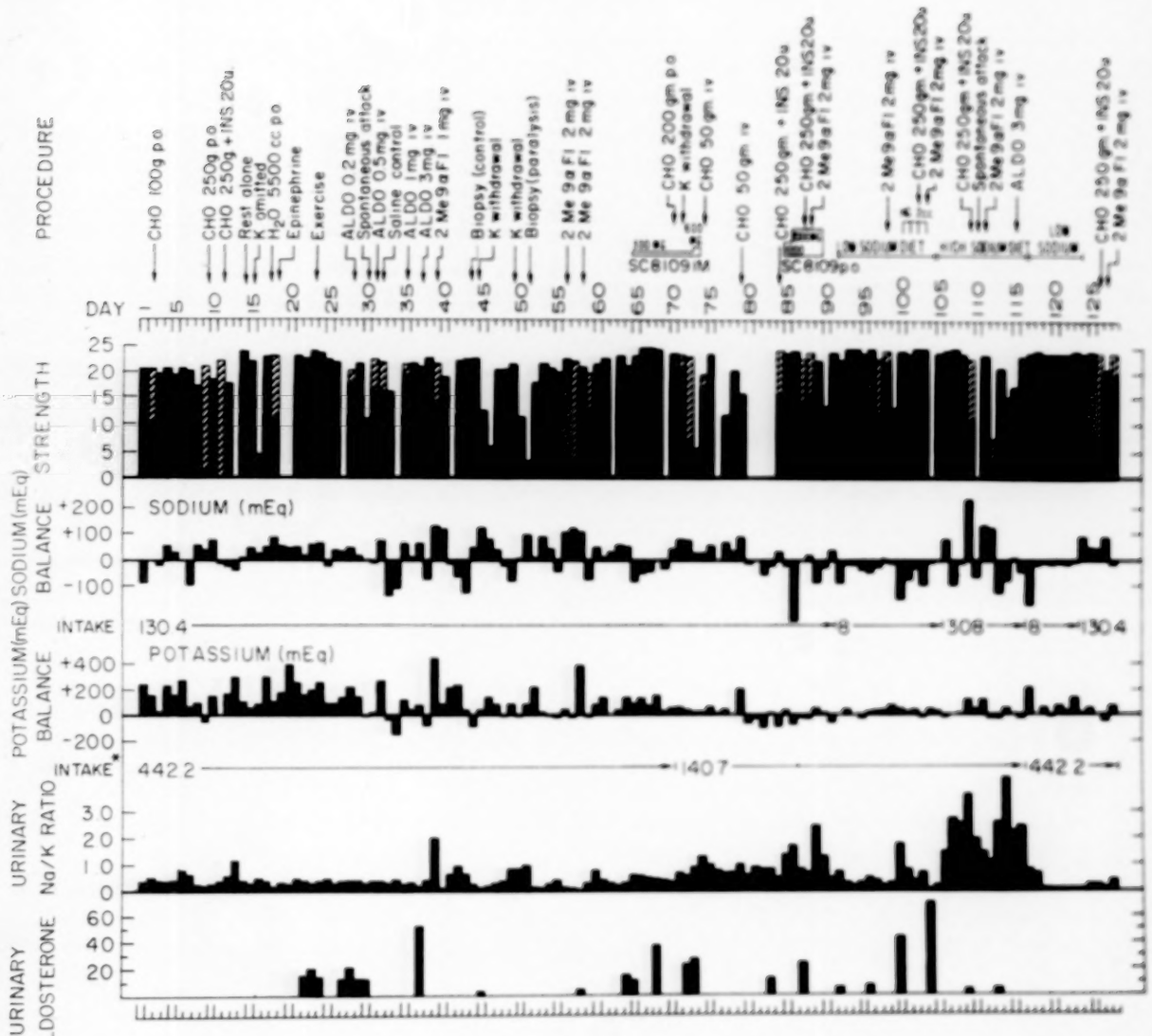
The patient's father, a fifty-two year old electrician had had attacks since childhood, which had become progressively less frequent. Examination revealed generally poor muscle development with marked atrophy of the thighs.

The patient's mother, his brothers aged thirty and twenty-six, and his sister aged twenty-eight, had been asymptomatic.

The diagnosis in this patient was therefore familial periodic paralysis. He lacked certain essential features of other familial syndromes manifested by paroxysmal paralysis, e.g., paramyotonia congenita, adynamia episodica hereditaria, acute intermittent porphyria and idiopathic paroxysmal myoglobinuria. Furthermore, hyperthyroidism, hyperadrenocorticism, hyperinsulinism and excessive gastrointestinal or renal loss of potassium, which are causes of sporadic paroxysmal paralysis, could be reasonably excluded as contributory causes in this patient.

METHODS

The muscular strength of the patient at a given time was evaluated by testing the sternomastoid, deltoid, iliopsoas and tibialis anterior muscles and grip strength bilaterally. This provided a sampling of the muscles of the neck and the proximal and distal muscles of the upper and lower extremities. The muscles chosen in each area were those most prone to weakness in this patient. Strength was rated from 0 (no contraction) to 5 (normal power) according to the method recommended by the British Medical Research Council [5]. All evaluations were made by the same examiner. Grip strength was measured in pounds using a hand dynamometer and in millimeters of mercury by squeezing a sphymgmomanometer bulb and converted to a single scale in arbitrary units ranging from 0 to 5 as shown in Figure 1. The ratings of each of the four muscle pairs and of grip strength



* On days 15, 44, 49, 56, and 70, the potassium intake was 341.7 mEq.; on days 45 and 50, 140.7 mEq.; on day 46, 542.7 mEq.; on days 79, 110, and 111, 241.2 mEq.; and on days 80 and 83, 191 mEq.

FIG. 2. Chart showing the sequence of drugs administered and changes in sodium and potassium intake and associated changes in muscular strength, in sodium and potassium "balances" and in urinary excretion of aldosterone. The shaded portion of each bar representing strength indicates the maximum degree to which strength decreased in that twenty-four-hour period; no entry for a given day indicates that strength was not tested on that day. The term "balance" here denotes intake minus the amount excreted in the urine; losses in feces and sweat were not estimated. CHO = glucose, INS = crystalline insulin, ALDO = *d,l*-aldosterone 21-monoacetate, 2 Me 9αFL = 2-methyl,9α-fluorohydrocortisone, Hg = meralluride.

were added, the maximum possible value being 25, and employed as an index of total muscle strength at a given time. Immediate retesting yielded the same value, indicating that the effort expanded in the testing procedure was not by itself sufficient to alter strength. The result for each day of the study, determined between 8 and 9 A.M. before rising or eating, is shown in Figure 2. Strength was tested more frequently when weakness was present or when experimental conditions were altered. The maximal degree of weakness observed is indicated for each day by shading on the same figure.

Twenty-four-hour urine collections were begun at 8 A.M. daily. The concentrations of sodium and potassium in serum and urine were determined by flame photometry. Selected urine specimens were also analyzed for aldosterone by the double isotope derivative method of Kliman and Peterson [6].

On days when 2-methyl,9α-fluorohydrocortisone was administered, the patient pursued his usual

schedule of meals and activity. On days when other test substances were employed, he was kept in bed fasting until the evening meal. In control experiments, remaining in bed by itself did not result in weakness; strength tested at two-hour intervals for eight hours varied less than 0.5 unit.

Injections were given and infusions begun on test days between 8 and 10 A.M. Crystalline preparations of 2-methyl,9α-fluorohydrocortisone (Upjohn) and *d,l*-aldosterone 21-monoacetate (Ciba) were dissolved in 2 cc. of absolute ethanol and administered intravenously in 100 cc. of 0.9 per cent sodium chloride over a two-hour period.

RESULTS

For the first twenty days of hospitalization the patient was asked to regulate his diet, intake of potassium chloride, exercise and rest as he would outside the hospital. His self-regulated program included an average daily intake of 2,000 calories (including 205 gm. of carbohydrate), 30 cc. of a 25 per cent aqueous solution of potassium chloride three times daily, two hours of active exercise and ten hours of bedrest. The carbohydrate intake represented self-imposed restriction because he had observed that the excessive intake of carbohydrate was followed by weakness. He kept his intake of potassium chloride at the minimum amount needed to function normally because it produced mouth irritation and epigastric distress. Notwithstanding his years of experience, self-regulation failed to prevent two attacks during which walking was difficult and two others which confined him to bed.

During the remainder of his hospitalization, the patient was asked to remain in bed between 10 P.M. and 8 A.M. and to exercise approximately the same amount daily. His diet contained 2,450 calories (including 250 gm. of carbohydrate) except for a two-week period during which it was reduced to 2,000 calories (including 200 gm. of carbohydrate) because of weight gain. On this regimen, during the following four months, he had only two attacks of any severity that appeared to be spontaneous. Under these conditions, diets of varying sodium content and drugs influencing the urinary excretion of sodium were administered; changes were noted in (1) muscular strength and (2) the effectiveness of glucose and insulin, 2-methyl,9α-fluorohydrocortisone, and potassium withdrawal separately in inducing weakness. The sequence of diets and drugs administered, and the resulting changes in muscular strength and urinary excretion of sodium, potassium and aldosterone are shown in Figure 2.

Variation in Morning Strength. Figure 1 shows the daily variation and the mean value for grip strength with the patient on daily sodium intakes of 130.4 mEq. (moderate), 8 mEq. (low) and 308 mEq. (high). Also studied, with the patient on an intake of 130.4 mEq. of sodium, was the effect of a drug antagonistic in action to aldosterone, 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl) propionic acid δ-lactone (SC-8109, Searle); 2,000 mg. per day was given orally in four equal doses. Spirolactones have been shown to increase the urinary ratio of sodium to potassium in the presence of aldosterone in animals [7] and in man [8]. Grip strength was increased by a low sodium intake and also by the administration of SC-8109 while on a moderate sodium intake. When on a high sodium intake the patient's grip strength tested at 8 to 9 A.M. was not significantly altered but grip strength tested at 3 A.M. was slightly reduced. Changes in index of total strength were less striking. (Fig. 2.)

Effect of Glucose and Insulin. Figure 3 shows the typical changes in strength with time following the administration of glucose, 250 gm. orally, and crystalline insulin, 20 units subcutaneously. A moderate intake of sodium (Fig. 3D) repeatedly resulted in marked weakness and a sinus arrhythmia. With a moderate intake of sodium combined with SC-8109 (Fig. 3C), or a low sodium diet alone (Fig. 3B), the administration of glucose and insulin produced less weakness and no arrhythmia. Intramuscular injections of 2 cc. of meralluride sodium, U.S.P. on the test day and on the two preceding days (Fig. 3A) increased the effectiveness of a low sodium intake. With a high sodium intake (Fig. 3E), although no marked weakness developed in eight hours, the patient became abruptly weak at the twelfth hour and the strength index was 0 from the eighteenth through the twenty-third hour. The cause for this delay in onset in weakness, if attributable to the testing procedure, is not clear.

Effect of 2-Methyl,9α-fluorohydrocortisone. Figure 4 depicts changes in muscle strength following the intravenous infusion of 2 mg. of 2-methyl,9α-fluorohydrocortisone in the late morning. Maximum weakness generally occurred from ten to twenty hours later. With the patient on a daily sodium intake of 130.4 mEq. (Fig. 4C), weakness was mild in degree. With a daily sodium

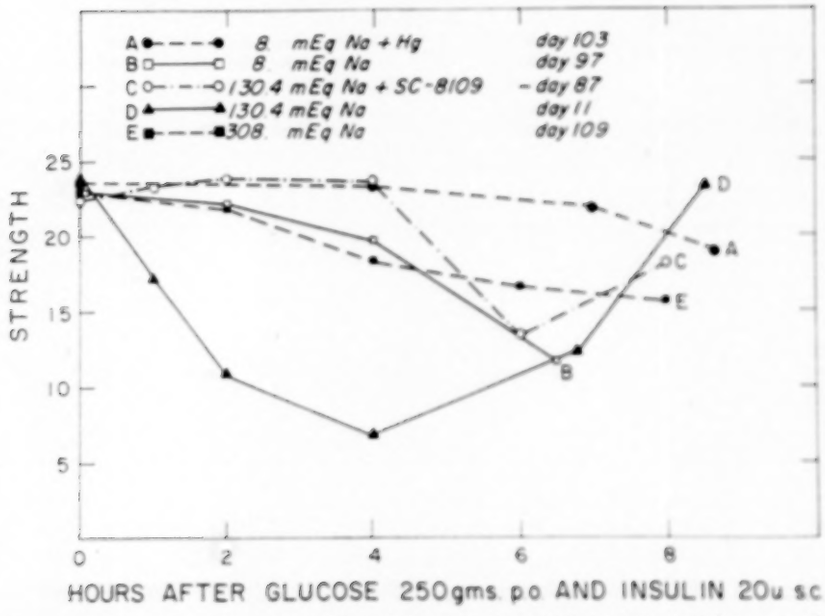


FIG. 3. Strength as a function of time following the administration of glucose and insulin under various circumstances of sodium loading and depletion.

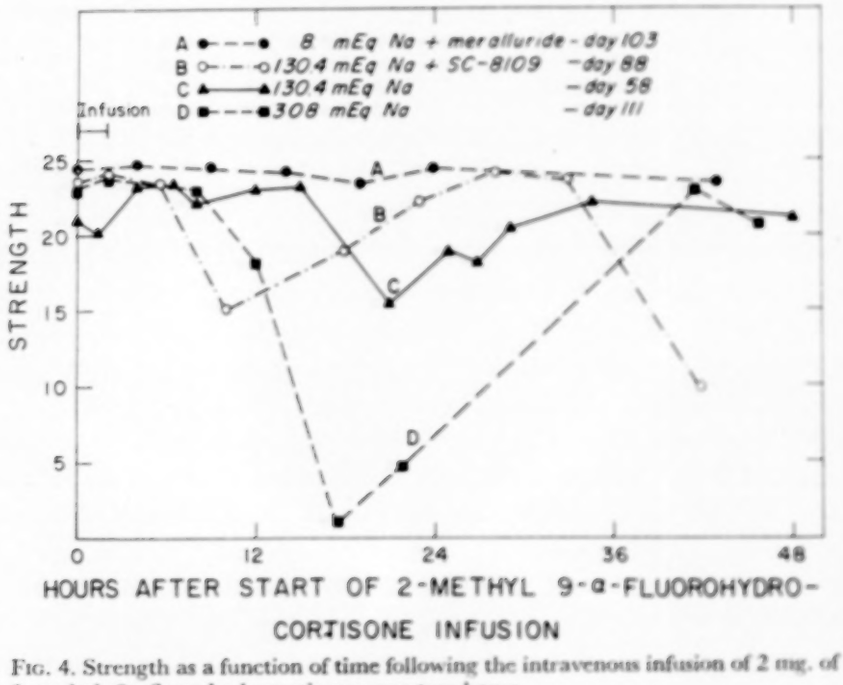


FIG. 4. Strength as a function of time following the intravenous infusion of 2 mg. of 2-methyl, 9α-fluorohydrocortisone over two hours.

intake of 308 mEq. (Fig. 4D), paralysis was virtually complete and sinus arrhythmia occurred. With a daily sodium intake of 8 mEq., when meralluride was given on the test day and on the preceding three days (Fig. 4A), there was no significant change in strength following the administration of fluorohydrocortisone. The patient's response on a low sodium diet without the addition of mercurials (not shown) was little different from that on a moderate sodium intake. When SC-8109 was combined with a moderate sodium intake (Fig. 4B), weakness appeared only after thirty-six hours, a result difficult to interpret.

Effect of Potassium Withdrawal. An effect of SC-8109 in preventing weakness following the

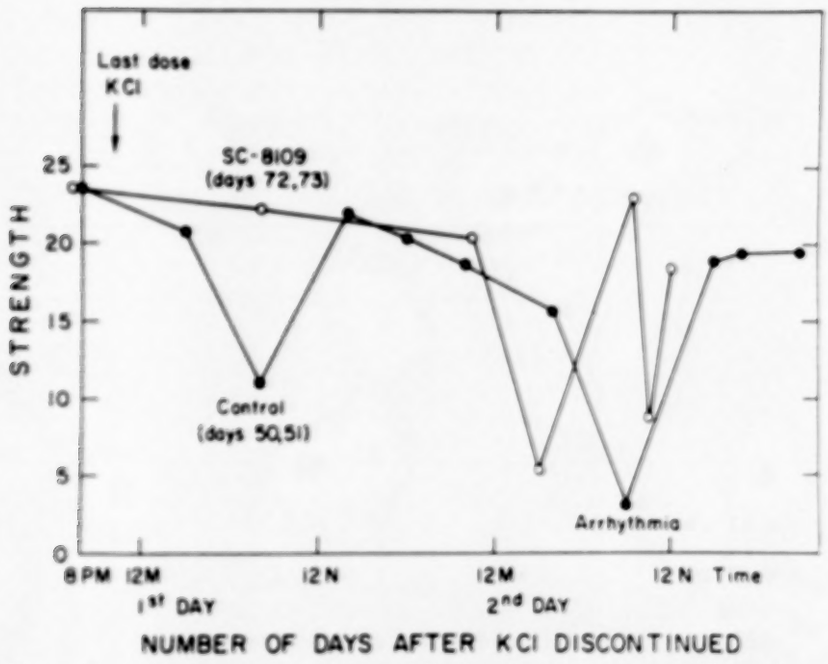


FIG. 5. Strength as a function of time following discontinuation of 25 per cent aqueous solution of potassium chloride, 30 cc., administered orally four times daily.

discontinuation of potassium chloride is suggested by the results depicted in Figure 5. On a sodium intake of 130.4 mEq., and without SC-8109, discontinuation of potassium chloride after the 10 P.M. dose resulted in moderate weakness on the first morning (day 50), nearly complete recovery later in the day, and nearly complete paralysis with sinus arrhythmia on the second morning. On the seventh day of therapy with SC-8109, 300 mg. per day administered intramuscularly in six equal doses, discontinuation of potassium chloride after the 10 P.M. dose was followed by no weakness on the first day (day 72) and less severe weakness without arrhythmia on the second day. Doubling the dose of SC-8109 on the second day failed to restore full strength.

Spontaneous Changes in the Severity of the Disease. Comparisons between the degree of weakness produced by a given procedure on two different days involves the assumption that there is no significant spontaneous change in the severity of the disease from day to day. Although this is unlikely to be exactly true, the responses to administration of glucose and insulin on days 9 and 126, and the responses to the intravenous administration of 2-methyl,9α-fluorohydrocortisone on days 58 and 127 (daily sodium and potassium intake being the same in all cases) were similar enough to suggest that the patient's disease was of comparable severity at the beginning and at the conclusion of the period of study.

Aldosterone Studies. Values for twenty-four–hour urinary aldosterone excretion under various conditions are listed in Table 1.

Aldosterone Excretion: Control Values. After acid hydrolysis the urine excreted by a normal adult on an *ad lib.* diet contains 5 to 20 μg. of aldosterone per twenty-four hours with a 50 per cent daily variation as determined by the double isotope derivative method by Kliman and Peterson [6]. The mean of the five control values obtained when this patient was normally strong and on a moderate sodium intake was 15.2 μg. The diurnal variation under control conditions was studied on one occasion when the total excretion was 12.1 μg. Sixty-four per cent of this total, or 7.7 μg., was excreted between 8 A.M. and 10 P.M. A normal person excretes about two-thirds of his total daily output of aldosterone between 7 A.M. and 7 P.M. [9]. Therefore, in the interval between attacks the total urinary excretion of aldosterone was normal and, on the occasion measured, the diurnal variation was not excessive.

Aldosterone Excretion: Effect of Diet and Drugs. As in the normal subject [10], aldosterone excre-

TABLE I
URINARY EXCRETION OF ALDOSTERONE

Day of Experiment	Condition	Aldosterone Excretion (μg./24 hr.)
22	Control	15
23	Control	20
24	Control	14
27	Control	12
28	*d,l*-aldosterone 0.2 mg. intravenously	21
29	Day preceding a spontaneous attack	12
30	Day of a spontaneous attack	12
38	*d,l*-aldosterone 3 mg. intravenously	53
45	Discontinuation of potassium chloride, 2nd day	2.4
58	2-methyl,9α-fluorohydrocortisone 2 mg. intravenously on days 56 and 58	4
64	Control	15
65	SC-8109, 300 mg./day intramuscularly 1st day	11
68	SC-8109, 300 mg./day intramuscularly 4th day	37
72	SC-8109, 300 mg./day intramuscularly 8th day	23
73	SC-8109, 600 mg./day intramuscularly	27
83	Control, total	12.1
	8 A.M. to 10 P.M.	7.7
	10 P.M. to 8 A.M.	4.4
87	SC-8109, 1,000–2,000 mg./day orally, 3rd day	24
100	8 mEq. sodium/day, 9th day, meralluride 2 cc. intramuscularly 1st day	44
104	8 mEq. sodium/day, 13th day; meralluride 2 cc. intramuscularly on days 100–103; 2-methyl,9α-fluorohydrocortisone 2 mg. intravenously on day 103	70
109	Day preceding a spontaneous attack; 308 mEq. sodium/day, 5th day	4
113	308 mEq. sodium/day, 9th day	5

tion fell when either potassium intake was sharply reduced (day 45) or a steroid with action similar to aldosterone was administered (day 58); it rose above normal when sodium was restricted and mercurial diuretics were administered (day 100). The excretion of 53 μg. following the intravenous administration of 3 mg. of aldosterone (day 38) is probably a normal response, for Ayres [11] found that a normal person on a moderate sodium intake excreted less than 5 per cent of a small dose of radioactive aldosterone given intravenously. On two occasions (days 68 and 87) aldosterone excretion rose following the administration of SC-8109, as might be expected following an aldosterone antagonist.

Aldosterone Excretion Prior to an Attack. Urinary aldosterone was elevated on neither the day of an apparently spontaneous attack (day 30) nor the day preceding two such attacks (days 29 and 109).

Effect of Aldosterone Infusion on Strength. While the daily sodium intake was 130.4 mEq., aldosterone infusion in 0.2, 0.5, 1, and 3 mg. amounts on separate days failed to produce changes in muscular strength significantly different from those when control infusions of saline without aldosterone were given. Sodium retention did occur on the days the two larger doses were administered indicating that the compound was active.

Confirmation of Findings in a Sibling. The nineteen year old affected brother of the patient was studied for a ten-day period. Each night before retiring he was permitted to take 100 mEq. of potassium chloride orally as had been his custom. On an *ad lib.* diet, morning strength was 21 units. The administration of 250 gm. of glucose orally and one hour later of 20 units of crystalline insulin subcutaneously was followed by a mild degree of weakness (strength 19 units) beginning one hour after the glucose and persisting for five hours. When the daily sodium intake was decreased to 8 mEq. for three days, morning strength increased to 23 units, but the response to glucose and insulin administered in the same manner was unchanged. The patient was then placed on a daily sodium intake of 308 mEq. and given 0.1 mg. of 2-methyl,9α-fluorohydrocortisone every eight hours. Forty-eight hours later the patient was almost totally quadriplegic (strength 0 units). Swallowing was subjectively difficult and vital capacity was 40 per cent of the control value. No spontaneous improvement occurred in the next seven hours. At the time, serum potassium was 1.8 mEq./L. and the electrocardiogram showed reduction in the amplitude of the T waves and prominent U waves. Improvement began in twenty minutes after the oral administration of 100 mEq. of potassium chloride and was complete in one hundred fifty minutes.

COMMENTS

A low serum potassium concentration during episodes of weakness was noted in familial periodic paralysis by Biemond and Daniels in 1934 [*12*]. Relief of the paralysis by the oral administration of potassium chloride was demonstrated by Aitken and his associates in 1937 [*13*]. Allott and McArdle [*14*] showed that potassium is retained in the body during attacks. From studies of the urinary excretion of water, nitrogen, creatine and creatinine during attacks, Ferrebee et al. [*15*] concluded that the potassium retention was not attributable to a general impairment of renal function. Since the fall in serum level was not due to renal loss, Allott and McArdle inferred that potassium entered the cells. They also noted that weakness occurred at serum potassium levels which in normal persons were unaccompanied by symptoms. They concluded that hypokalemia was only one factor in producing weakness, an abnormality of the neuromuscular apparatus being another. McArdle [*16*] found that on a normal potassium intake, ACTH precipitated severe attacks, whereas on a higher intake of potassium the same dose of ACTH had little effect.

Zierler and Andres [*17*] showed the uptake of potassium from arterial plasma by skeletal muscle to be increased several fold during the development of a nocturnal attack induced by the administration of glucose and insulin. Potassium moved out of skeletal muscle at several times the normal rate for that time of day during the spontaneous recovery from a spontaneous nocturnal attack and also during recovery, induced by oral potassium chloride, from an attack induced by glucose and insulin. One subject was studied on two separate occasions while asymptomatic, and a normal nocturnal movement of potassium into muscle was measured. Zierler and Andres suggested that the characteristic onset of attacks during the night with spontaneous recovery later in the morning may result from an exaggeration of the normal diurnal variation in net potassium movement between muscle and plasma.

Grob, Johns and Liljestrand [*18*] determined that the shift of potassium from plasma to muscle was greater for a given dose of glucose or of epinephrine in three patients with familial periodic paralysis than in the normal subject. They also found that insulin, which causes potassium to leave muscle in normal persons, causes potassium to enter muscle in patients with periodic paralysis.

Goldflam in 1897 [*19*] described central vacuoles in muscle fibers from patients with familial periodic paralysis. Conn [*2,3*] noted that on a high sodium diet the muscle from one patient showed vacuoles and an abnormally high sodium concentration per wet weight of muscle, but on a low sodium diet the muscle showed no vacuoles and a lower sodium concentration.

Vastola and Bertrand [*20*] analyzed muscle during and between attacks. During a spontaneous attack they found a marked increase in extracellular and intracellular water, a marked increase in the absolute amount of intracellular potassium referred to muscle solid, due in large part to a shift from non-muscle tissues, and an increase in the ratio of concentrations of intracellular to extracellular potassium in association with the fall in extracellular potassium concentration.

Conn in 1957 [*2,3*] reported findings which he interpreted to indicate that the increased sodium in the muscle was partially responsible for the disturbance of muscle function. First, on a daily sodium intake of 208 mEq., the oral administration of 150 gm. of glucose and 20 units of insulin or of 1 mg. of 2-methyl,9α-fluorohydrocortisone produced complete and prolonged quadriplegia, whereas on a daily sodium intake of 8 mEq., these measures failed to produce an attack. Second, the earliest return of muscle function was related temporally to increasing amounts of urinary sodium. Third, the total body exchangeable sodium was elevated before induction of an attack and increased considerably during the induction of an attack. Fourth, during an attack sodium per gram of wet muscle, compared to the normal, was elevated, whereas during sodium restriction when the patient had no attacks, sodium was either less elevated or normal. This evidence, together with the previously reported decreased urinary sodium preceding attacks, elevated serum sodium during attacks, and increased urinary sodium excretion following attacks suggested a prominent role for sodium in the pathogenesis of the paralysis.

In addition, Conn has reported that spontaneous attacks and those induced by the ingestion of glucose and insulin are preceded by large increases in urinary aldosterone and that, during the intense sodium diuresis which follows, urinary aldosterone falls below normal. Furthermore, attacks could be precipitated, provided

sodium intake was not severely restricted, by a synthetic steroid with physiologic action similar to aldosterone, *viz.*, 2-methyl,9α-fluorohydrocortisone. For these reasons Conn suggested that spontaneous attacks of paralysis and those induced by means other than administration of a synthetic steroid are due to "intermittent aldosteronism."

In a patient with sporadic idiopathic periodic paralysis, Eales [*20*] found that, after chlorothiazide therapy following prolonged sodium restriction, there were neither spontaneous attacks nor attacks following the administration of glucose and insulin or 9α-fluorohydrocortisone.

The present study confirms the contention of Conn that in familial periodic paralysis a high sodium intake predisposes toward, and a low sodium intake protects against, weakness, whether spontaneous or induced. That 2-methyl,9α-fluorohydrocortisone can produce typical attacks was substantiated as well. Agents which increase sodium excretion also protect against weakness; the present study has confirmed this finding for a mercurial diuretic and has extended it to a spirolactone, SC-8109.

No evidence was found, however, for a primary disturbance of aldosterone metabolism in this disease, as suggested by Conn. The patient studied resembled the normal person in his total daily excretion, his diurnal variation and his responses to potassium withdrawal, to mineralocorticoid administration and to the administration of aldosterone itself. The twenty-four–hour urinary excretion was elevated neither on the day of one apparently spontaneous attack nor on the days just preceding two such attacks. Finally, the administration of aldosterone, in doses up to 3 mg. intravenously, failed to induce attacks of weakness even with the patient on a high sodium intake.

Two pertinent queries have been raised elsewhere [*22*] concerning this theory. If aldosterone change is the primary event, why is the sodium retention not accompanied by massive loss of potassium in the urine, as in sustained primary aldosteronism? If spontaneous attacks are the result of intermittent primary hyperaldosteronism, why are they more apt to occur at night when aldosterone secretion is lowest?

The retention of sodium and water, which occurs during an attack of paralysis, is a characteristic feature of the disease and demands an explanation. The presence of a mineralocorticoid in excessive amounts is a possible explanation, but no primary disturbance of aldosterone metabolism was observed during this study. Furthermore, when secondary hyperaldosteronism was induced by various stimuli no weakness appeared. The extraction studies of Grob, Liljestrand and Harvey indicate an inherent abnormality in the muscle. They showed that the permeability of the muscle membrane to glucose, epinephrine and insulin is abnormal. Whatever its ultimate basis, whether an abnormal structure of the muscle membrane or an intracellular metabolic defect, most features of periodic paralysis with hypokalemia are attributable to an excessive response to stimuli that promote the entrance of potassium into muscle fibers in normal persons. The excessive response in these subjects is in some way aggravated by sodium loading and minimized by sodium depletion.

A low sodium diet may then be more rational therapy than potassium salts in familial periodic paralysis. Potassium excretion involves secretion by the renal tubules in exchange for sodium ion absorption, and the retention of excess sodium has already been shown deleterious to muscle strength.

SUMMARY

1. Two patients with familial periodic paralysis were investigated with regard to the effect of sodium loading and depletion on muscular strength and on resistance to measures disposing to muscular weakness. Sodium loading was achieved by dietary excess or by administration of 2-methyl,9α-fluorohydrocortisone. Sodium depletion was accomplished by dietary restriction or by administration of a mercurial diuretic or SC-8109, a spirolactone with an action antagonistic to aldosterone.

2. Sodium loading was in general associated with a decrease, and sodium depletion associated with an increase in strength and in resistance to measures disposing to weakness.

3. Urinary aldosterone excretion, measured by a double isotope derivative technic, was normal prior to two spontaneous attacks, and, as in normal persons, rose with sodium depletion, and fell with sodium loading.

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Megaloblastic Anemia Associated with Anticonvulsant Drugs*

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IN 1952 Mannheimer and his associates [*1*] in reviewing hematological complications of antiepileptic therapy with hydantoin derivatives described a patient in whom a "pernicious anemia-like" disorder developed with megaloblastic marrow. Prolonged therapy with large amounts of vitamin B_{12} was required to restore the blood picture to normal. In 1954 Badenoch [*2*] described two cases of megaloblastic anemia associated with anticonvulsant drug therapy. We are aware of an additional fifty-three reported cases [*3–30*]. Reviews of this subject have appeared elsewhere [*17,27*]. Diphenylhydantoin sodium (Dilantin®), primidone (Mysoline®) and phenobarbital derivatives have been incriminated singularly or in various combinations.

The pathogenesis of this disorder remains obscure. The most striking hematological responses have been obtained with folic acid therapy. In some patients, vitamin B_{12} therapy alone produced satisfactory results. The biochemical structural similarity of these anticonvulsants to the pterodyl portion of folic acid has led to the suggestion that they may interfere with the metabolism of folic acid [*12*]. Gydell has suggested that a subclinical nutritional deficiency may be a predisposing factor [*17*].

The present report describes two cases of megaloblastic anemia associated with the use of Dilantin and barbiturate derivatives. Detailed nutritional studies revealed evidence of multiple deficiencies in both patients. One of these patients was reported on in abstract elsewhere [*31*]. In this patient complete hematological remission was obtained with the oral administration of folic acid, 500 μg. per day, even in the face of continued anticonvulsant drug therapy and dietary inadequacy.

SPECIAL LABORATORY METHODS

Serum and urinary folic acid‡ activity was assayed using Streptococcus fecalis strain 29-21 according to the procedure of the Association of Official Agricultural Chemists (AOAC) [*32*]. The modified AOAC medium described by Brodovsky, Utley and Pearson was employed [*33*]. The folic acid tolerance test was carried out by the technic of Clark [*34*]. Urinary formiminoglutamic acid excretion was determined according to the technic of Bakerman and his associates [*35,36*] as modified by Seegmiller and his co-workers [*37*]. Serum vitamin C concentrations were measured by a modification of the dye method (2,6-dichloro-benzenone-indophenol) of Bessey and Pinkerton [*38*], and serum vitamin A and carotene concentrations by an adaptation of the method of Carr and Price [*39*]. Vitamin B_{12} absorption was tested according to the method of Schilling [*40*]. Serum vitamin B_{12} activity was determined by assay with the protozoan, Euglena gracilis, according to the technic of Ross [*41*]. The d-xylose absorption test was performed by the method of Benson and his associates [*42*].

CASE REPORTS

CASE 1. A twenty year old white plumber's helper was admitted to the Vanderbilt University Hospital in March 1956 because of recurrent abdominal pain of two years' duration. In 1952 a diagnosis of psychomotor epilepsy had been made and maintenance treatment with Dilantin 0.3 gm., mephobarbital (Mebaral®) 0.2 gm. and phenobarbital 0.1 gm. per day was instituted.

In 1954 the patient noted the onset of episodes of cramping lower abdominal pain. The attacks lasted from one to twenty-four hours, occurred about twice a month and were accompanied by mild nausea and "acid regurgitations." There were no vomiting, diarrhea, sore tongue, change in bowel habits or abnormalities of the stool. An "interval" appen-

‡ Pterodylglutamic acid.

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dectomy in 1955 was followed by temporary relief from these symptoms for approximately six months. There were also sporadic episodes of fever and arthritis, the latter involving the proximal interphalangeal joints of both hands. The past and family histories were non-contributory.

The patient was an asthenic white man, who did not appear obviously malnourished. He weighed 120 pounds. The temperature was 98.6°F. The skin was pigmented as if sun tanned, dry and slightly scaly. The tongue appeared normal. Examination of the heart and lungs was within normal limits. The pulse rate was 92 beats per minute, and the blood pressure, 130/70 mm. Hg. The remaining salient features of the examination were: gingival hypertrophy, slight thickening of the proximal interphalangeal joints of the fingers and palpable enlargement of the liver and spleen (each 3 to 4 cm. below the costal margins). Neurological examination did not disclose any abnormalities.

Results of urinalysis and serological tests for syphilis were negative. Blood examination revealed volume of packed red cells 34.5 per cent, red cells 3.09 million per cu. mm., hemoglobin 11.8 gm. per 100 ml., reticulocytes 0.5 per cent, white cells 3,200 and platelets 48,000 per cu. mm. The mean corpuscular volume (MCV) was 112, mean corpuscular hemoglobin (MCH) 39, and mean corpuscular hemoglobin concentration (MCHC) 34. The white cell differential count revealed: segmented neutrophils 80 per cent, lymphocytes 17 per cent, and monocytes 3 per cent. Serum bilirubin was 0.3 mg. per cent. Marrow aspiration smears were moderately hypocellular but otherwise not remarkable. The following laboratory tests yielded normal results: L.E. cell tests, urinary porphobilinogen and uroporphyrins, serum electrolytes, liver function tests, blood and marrow cultures, and febrile agglutination tests. The serum cholesterol was 115 mg. per cent. Chest roentgenogram, gastrointestinal series and barium enema were all within normal limits.

The nine-day hospital course was characterized by periodic low grade fever. The patient was discharged without a specific diagnosis with instructions to continue on the same anticonvulsant drug regimen. He improved spontaneously, gained weight and returned to work.

The patient was readmitted in May 1957 for recurrence of episodic abdominal pain and increasing weakness of three weeks' duration. For the past several months he had noted progressive anorexia and mild nausea. Apparently the original weight gain of 20 to 30 pounds was cancelled by a similar loss during the several months prior to admission.

The patient appeared chronically ill as well as in acute distress due to abdominal pain. The weight was 124 pounds. The temperature was 99.4°F. On physical examination all the findings noted during the first admission were present; in addition there was evidence of more pallor and a grade 2 blowing systolic murmur over the precordium. Again the neurological examination demonstrated no abnormalities.

Initial blood counts revealed volume of packed red cells 18.2 per cent, red cells 1.8 million per cu. mm., hemoglobin 6.1 gm. per 100 ml., reticulocytes 0.6 per cent, white cells 1,700 and platelets 22,000 per cu. mm. The red cell indices were MCV 201, MCH 34 and MCHC 34. Differential leukocyte count showed 2 per cent myelocytes, 1.5 per cent juvenile neutrophils, 83 per cent segmented neutrophils, 2 per cent eosinophils, 11 per cent lymphocytes and 0.5 per cent monocytes. There were moderate macrocytosis, anisocytosis and poikilocytosis of the red cells. Marrow aspiration smears revealed a typically megaloblastic pattern. The bleeding time was 17 minutes, and the result of the Rumple-Leede tourniquet test was positive. The coagulation time was normal. The direct and indirect Coombs' tests were negative. The serum bilirubin was 0.3 mg. per cent, the cephalin flocculation test 4 plus, and the serum cholesterol 110 mg. per cent. Otherwise liver function tests and serum electrolytes were normal. Again tests for urinary porphyrins were negative. The chest roentgenogram, intravenous pyelogram, and gastrointestinal series with small bowel study were all within normal limits.

Because of severe anemia and weakness the patient was given 1,000 ml. of whole blood which elevated the hematocrit to 24 per cent. (Fig. 1.) The dietary history and detailed nutritional studies obtained at this time revealed evidence of deficiencies of folic acid, vitamin C, vitamin B_{12} and possibly carotene (see also section on "Special Nutritional Studies"). The patient's course is shown in Figure 1. On the ninth hospital day oral folic acid therapy, 500 μg. per day, was started. The anticonvulsant drug regimen and dietary habits were purposely continued unchanged. On the eighth day of treatment the reticulocytes reached a peak of 9.5 per cent. There was a striking improvement in appetite and sense of well-being within three days. Fever disappeared on the fourth day. Hematological improvement was dramatic. (Fig. 1.) The patient was discharged improved on June 6 (fourteenth day of treatment) with instructions to continue the same folic acid and antiepileptic therapy and the same inadequate diet. At the time of discharge volume of packed red cells was 35 per cent, red cells 3.48 million per cu. mm., hemoglobin 10.1 gm. per cent, white cells 4,000 and platelest 236,000 per cu. mm.

The patient returned by appointment on July 11 (forty-ninth day of treatment). There had been a dramatic return of strength and sense of well-being to normal, and he had worked regularly. He now weighed 150 pounds, representing a 26 pound gain since the institution of folic acid therapy. Physical examination was within normal limits. The blood counts and blood and bone marrow smears were

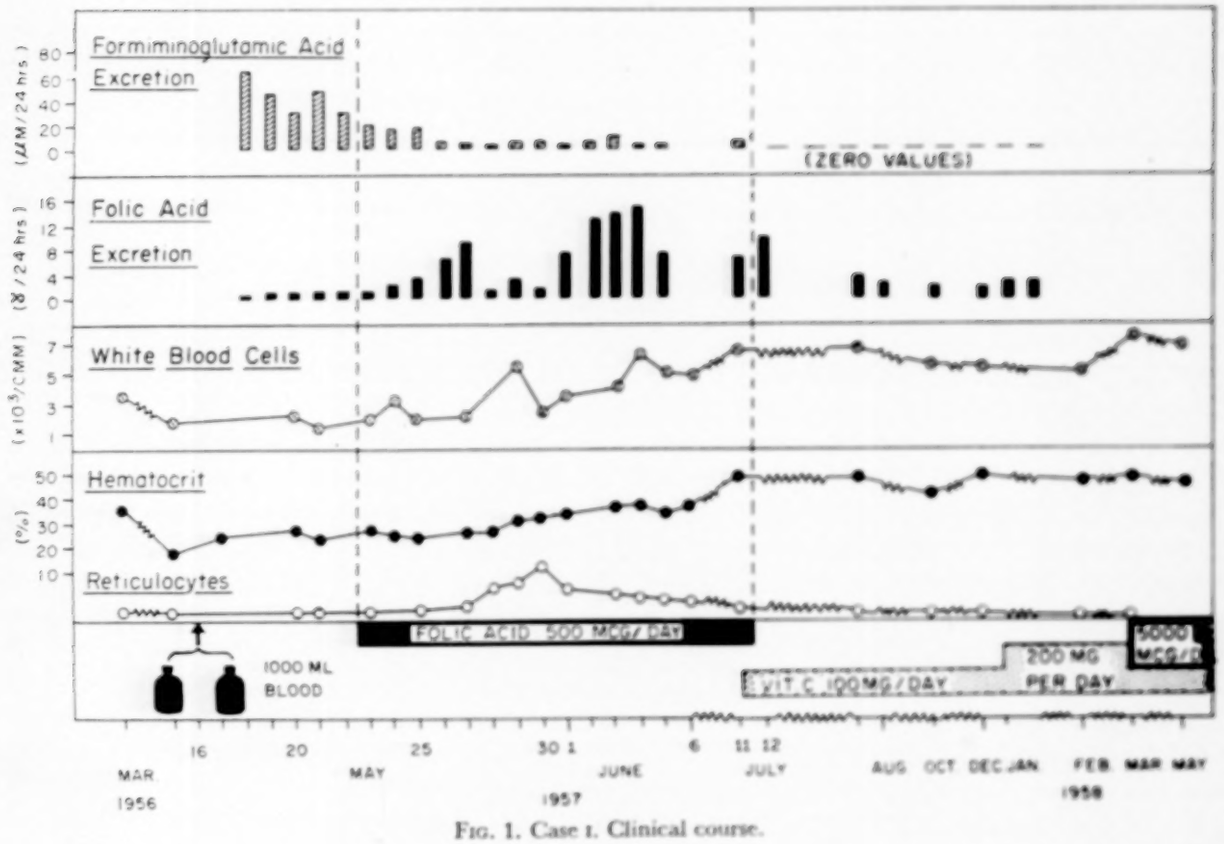

FIG. 1. Case 1. Clinical course.

entirely normal. The cephalin flocculation test was now normal as were the other biochemical tests of liver function. Oral folic acid therapy was discontinued. In view of biochemical evidence of persisting ascorbic acid deficiency, oral vitamin C therapy, 100 mg. per day, was instituted.

The patient has since been seen at one to two month intervals for hematological and nutritional studies. He remains in good health and works regularly. He was readmitted on December 30, 1957, for further nutritional investigation (see section on "Special Nutritional Studies"). The dark brown cutaneous pigmentation was still present. Otherwise the physical examination was within normal limits. Sigmoidoscopic examination revealed no abnormalities. Oral vitamin C therapy was increased to 200 mg. per day.

Oral folic acid therapy was reinstituted at a dose of 5 mg. per day in March 1958. When last seen in July 1959 the patient was in excellent health. Blood counts have remained normal. He has continued on the regimen of oral folic acid, vitamin C and anticonvulsant drugs and remains on the same inadequate diet.

SPECIAL NUTRITIONAL STUDIES

Dietary History. As an infant, skin rashes developed following the ingestion of citrus juices, and therefore the patient was given ascorbic acid tablets until the age of seven years. Thereafter, he took neither fruit juices nor ascorbic acid. He also avoided leafy green vegetables and "organ meats," the other chief dietary sources of vitamin C and folic acid. With respect to dietary sources of vitamin B_{12}, the patient did eat cheese about twice weekly, and meat and eggs daily, but he did not drink milk.

Folic Acid. The striking increase in urinary folic acid excretion during the initial course of oral folic acid therapy (500 μg. per day) is shown in Figure 1. Prior to treatment the values were 0.5 to 1.2 gamma per twenty-four hours. During treatment, values as high as 14.3 gamma per twenty-four hours were obtained. Evidence has been cited that formiminoglutamic acid is excreted in large amounts in folic acid deficiency states, and that this excretion falls to negligible values when folic acid therapy is instituted [*43–45*]. Figure 1 demonstrates that such was the case in our patient.

In June 1957 the serum folic acid concentrations showed a normal rise following the oral administration of 1 mg. of this compound. (Fig. 2.) When the test was repeated following

the oral administration of 5 mg. of folic acid daily for one week, there was an even greater rise in the serum folic acid concentration. These findings suggest a greater saturation of body stores at the time of the second test.

Vitamin C. The serum vitamin C concentrations were abnormally low on admission (May 1957) and remained so during and after the initial hematological response. (Fig. 3.) Vitamin C tolerance tests showed flat curves in June and August 1957 despite the fact that oral vitamin C, 100 mg. per day, had been administered for four days prior to the latter test. Only when a "saturating dose" of 3,000 mg. was given over a three-day period did the serum vitamin C concentration become normal. (Fig. 3.) These data suggest that the initial, scorbutic-type tolerance tests were due to failure to provide adequate saturation of body stores, and that there was no evidence of malabsorption of vitamin C.

Vitamin A and Carotene. With the exception of one determination (June 1957) serum vitamin A concentrations were within the normal range. (Fig. 3.) A vitamin A tolerance test performed at this time showed a flat curve (abnormal response). However, a repeat test in January 1958 demonstrated a normal response. Serum carotene concentrations were low which may merely reflect a poor dietary intake of this nutrient.

Vitamin B_{12}. Gastric analysis revealed 37° free and 57° total acidity after histamine stimulation. Serum vitamin B_{12} concentrations were 50 and 73 μμg. per 100 ml. on May 17 and June 6, 1957, respectively (normal value: greater than 100 μμg. per 100 ml.). In November 1958 the value was 124 μμg. per 100 ml. On no occasion was there any "free" serum vitamin B_{12}. A Schilling test performed in January 1958 revealed 30 per cent urinary excretion of the orally administered radioactivity.

Studies Regarding Malabsorption. Results of the oral glucose tolerance test were normal. Radiological studies of the upper gastrointestinal tract and small bowel were within normal limits. Stool fat analysis revealed 6.4 per cent (wet weight) fat in a pooled four-day specimen. Oral d-xylose absorption tests showed a normal two-hour serum concentration with a somewhat reduced five-hour urinary excretion. (Fig. 4.) The two-hour serum concentration has been considered a much more reliable criterion than the five-hour urinary excretion [*42*].

These data provide evidence against any significant absorptive defect to account for the deficiency state in our patient. The normal vitamin C tolerance test after adequate saturating doses and the normal vitamin A and folic acid tolerance tests provide further evidence against any absorptive defect.

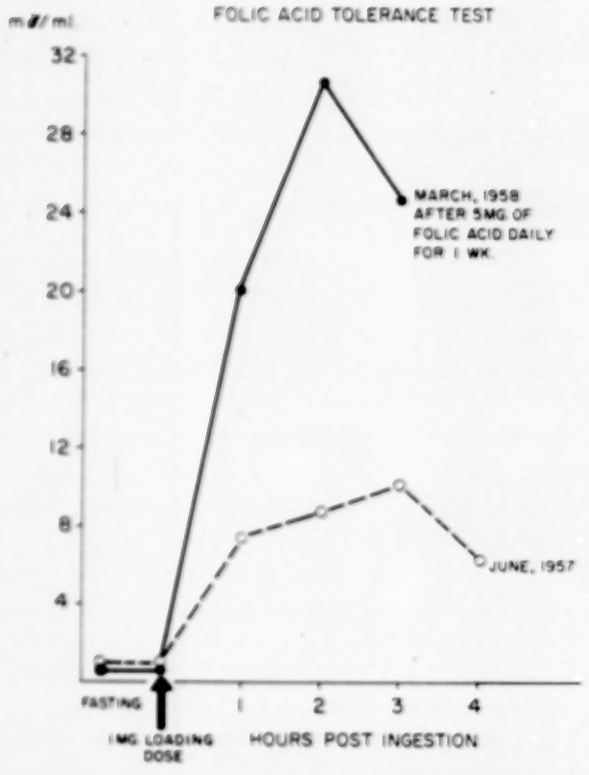

FIG. 2. Case I. Folic acid tolerance tests showing serum concentrations following the oral ingestion of 1 mg. of folic acid. The test of June 1957 was obtained on the fifteenth day of treatment with oral folic acid, 500 μg. per day. The test of March 1958 was obtained following a larger, "saturating dose." Both responses are normal, but that following the "saturating dose" is distinctly greater.

Studies on Patient's Mother. The patient's mother likewise had dark brown skin but was in good health. Her dietary history was essentially normal. Blood counts and serum vitamin A and C and carotene concentrations were normal.

CASE II. A thirty-one year old white semi-invalid man entered the Vanderbilt University Hospital for the fifteenth time in March 1952 because of persistent nausea, anorexia and the vomiting of bright red blood. The patient was first seen in 1939 for drainage of a cerebral abscess. Following this procedure there were five subsequent hospitalizations for recurrent bacterial and fungus infections of the wound site. The patient sustained permanent neurological damage which left him with a right hemiplegia and a right-sided sensory loss. There were also impaired coordination and mentation.

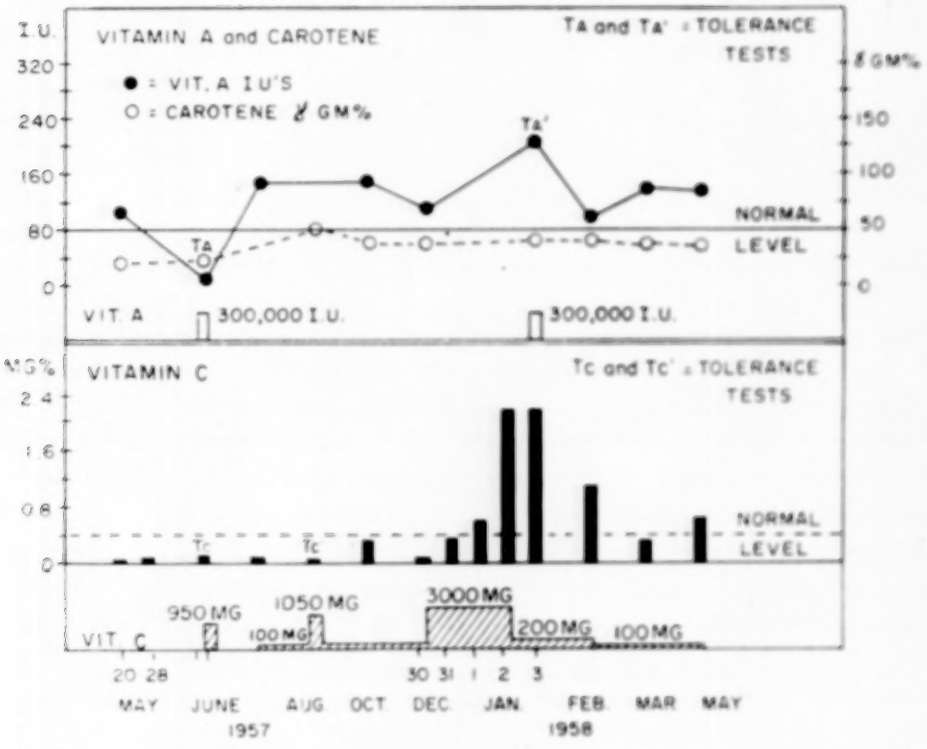

FIG. 3. Case 1. Serum concentrations of vitamins C and A and carotene. "Normal level" indicates the minimum normal serum concentrations. T_A, $T_{A'}$, T_C and $T_{C'}$ indicate the dates of vitamin A and C tolerance tests. See section "Special Nutritional Studies" for results of the tolerance tests.

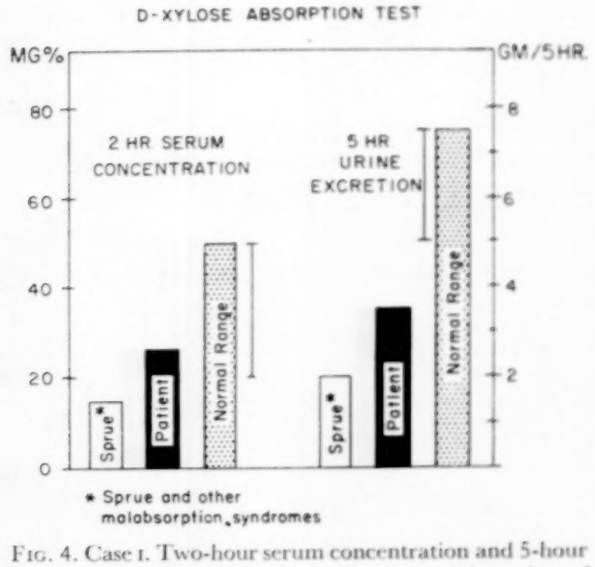

FIG. 4. Case 1. Two-hour serum concentration and 5-hour urinary excretion of d-xylose following the ingestion of 25 gm. of the compound. Values for normal subjects and for patients with sprue and other malabsorption syndromes were taken from those published by Benson and his associates [42].

In 1945 he was admitted for the first of many grand mal seizures. At this time he was given 0.1 gm. each of Dilantin and phenobarbital daily. With exception of increases during brief hospitalizations for control of the seizures, these amounts of anticonvulsant drugs have been continued to the present. In 1951 the patient experienced rather profuse blood loss and a fall in hemoglobin following dental extractions. He was placed on oral iron therapy and supplementary multiple vitamins for approximately one month with a good hematological response.

At the time of admission in 1952, the symptoms of nausea, vomiting and anorexia had been present for six months. The patient was an afebrile, well developed and seemingly well nourished twenty-six year old hemiparetic in no acute distress. The skin and mucous membranes were pale. There was cheilosis, but there were no lesions of the buccal mucosa. The gums were not hypertrophied, and the tongue showed no papillary atrophy. Expressive aphasia was evident, the speech being slow and hesitant. Examination of the chest and cardiovascular system was within normal limits. The liver and spleen were not palpable. Neurological examination demonstrated a homonymous hemianopsia with a lateral nystagmus. There was total loss of sensory modalities on the right, and the right hand and arm were ataxic, flexed and contracted.

Results of serological tests for syphilis and urinalysis were negative. Blood examination revealed the volume of packed red cells to be 23 per cent, red blood

cells 2.4 million per cu. mm., hemoglobin 8 gm. per cent, white cell count 3,300 and platelet count 108,000 per cu. mm. Red cell indices revealed MCV 96, MCH 33 and MCHC 35. The differential leukocyte count showed 39 per cent segmented neutrophils, 59 per cent lymphocytes and 2 per cent monocytes. Polychromatophilia and anisopoikilocytosis were noted on the blood smears. Bone marrow aspiration smears were stated to be normal. Total serum bilirubin was 1.3 mg. per cent with 1.1 indirect. Serum proteins and electrolytes were within normal limits. No gastrointestinal pathologic condition could be demonstrated on roentgenograms of the upper gastrointestinal tract, small bowel and barium enema. The patient was given a transfusion of 1,000 ml. of whole blood and discharged.

The patient continued to complain of gastrointestinal discomfort and was seen intermittently over the next four years for this reason. In September 1956 he was again hospitalized because of anemia. The only new physical finding was gingival hypertrophy. The liver and spleen were again impalpable and results of the neurological examination were unchanged. Blood examination revealed the volume of packed red cells to be 27 per cent, red cells 2.7 million per cu. mm., hemoglobin 8.9 gm. per cent, reticulocytes 1 per cent, white cells 3,900 and platelets 90,000 per cu. mm. The red cell indices were MCV 100, MCH 35 and MCHC 33. The differential leukocyte count showed 3.5 per cent juveniles, 74.5 per cent segmented neutrophils (11.5 per cent hypersegmented forms), 2.5 per cent eosinophils, 16.5 per cent lymphocytes and 3 per cent monocytes. There was moderate anisopoikilocytosis of the erythrocytes. Bone marrow aspiration smears revealed a typically megaloblastic pattern. Liver function studies, serum bilirubin and cholesterol, prothrombin time, serum total protein, and osmotic fragility of the red blood cells were normal. The serum concentrations of vitamins A and C, and carotene were low (see section on "Special Nutritional Studies").

Therapy with oral folic acid, 15 mg. daily, resulted in striking improvement in appetite and sense of well-being within several days. By the tenth day reticulocytes had reached a peak of 13 per cent, and the white cell and platelet concentrations had returned to normal values. Subsequent marrow aspiration smears were normal. Folic acid therapy was discontinued after thirty days. When the patient was last seen in January 1960 the blood counts and red cell indices were normal. His neurological abnormalities continued unchanged, and maintenance anticonvulsant drug therapy was required to control the seizures.

SPECIAL NUTRITIONAL STUDIES

Dietary History. Since the onset of his neurological difficulties in 1939, the patient's eating habits have been extremely abnormal. The diet has consisted almost exclusively of carbonated beverages, cheese, crackers and candy. Occasionally the patient ate chicken, potatoes and green beans (the only green vegetable) for "Sunday dinner." There was little or no desire for food, especially for fruits or fresh vegetables. Thus the dietary analysis revealed poor intakes of folic acid, vitamin C, protein and of some of the vitamin B complex.

Folic Acid. In September 1958, the fasting serum folic acid concentration was 1 μμg. per 100 ml. Following the oral ingestion of 1 mg. of folic acid, the serum concentration rose to 52 μμg. in one hour, followed by a gradual fall to 8 μμg. in four hours. The patient had previously been receiving 5 mg. of folic acid daily for one week. According to Clark these data would constitute a normal reaction to the folic acid tolerance test [*31*].

Vitamin C. In January 1957 fasting vitamin C level was 0.07 mg. per cent, a value well below normal. A vitamin C tolerance test performed in September 1958 revealed a similarly low fasting level of 0.03 mg. per cent, but a normal rise to 0.52 mg. per cent in one hour and a peak of 0.98 mg. per cent in three hours. This test, therefore, revealed a low serum concentration with but slight desaturation of body stores.

Vitamin A and Carotene. Studies in September 1956 revealed a normal fasting serum vitamin A concentration of 113 I.U. per 100 ml. as well as a normal vitamin A tolerance test. A repeat study in September 1958 likewise yielded normal results. On both of these occasions the dietary history of poor carotene intake was confirmed by abnormally low serum carotene concentrations (25 to 41 μg. per cent).

Vitamin B_{12}. Repeated gastric analyses have revealed free hydrochloric acid after histamine stimulation. The Schilling test in January 1958 demonstrated 20 per cent excretion of the orally administered radioactivity in twenty-four hours. Serum vitamin B_{12} concentration was determined only after the Schilling test (November 1958) and was normal (228 μμg. per 100 ml.).

Serum Iron Studies. One determination in September 1956 revealed a serum iron concentration of 28 μg. per cent with a residual iron binding capacity of 370 μg. per cent and 7 per cent saturation of the iron binding protein.

Studies Regarding Malabsorption. Roentgenograms of the upper gastrointestinal tract and small bowel were normal on two occasions. Results of the oral glucose tolerance test were

normal. In May 1959, fat absorption studies using I^{131}-labelled triolein were within normal limits.

COMMENTS

Dilantin has been used as an antiepileptic drug since 1938, primidone since 1951, and phenobarbital for many decades. It is curious that among the countless patients receiving these drugs less than sixty cases of megaloblastic anemia have been documented [*1–30*]. The first case was described in 1952 in association with Dilantin, fourteen years after the introduction of this drug. Surveys, comprising a combined total of 534 patients treated with these drugs, revealed only four definite cases of megaloblastic anemia in which other possible causes were eliminated [*7,8,16,27*].

Forty-seven of the fifty-eight cases of anticonvulsant megaloblastic anemia have been reported from the British Isles. Only two previous cases have been described from American clinics [*10,19*]. Of the fifty-two cases in which the sex and age were given, 39 or 75 per cent were female. In contrast to the age distribution in Addisonian pernicious anemia, in thirty-nine cases the age was less than forty years at the time of diagnosis. The youngest case was that in a seventeen year old female [*14*].

Girdwood and Lenman suggested that these anticonvulsant drugs may antagonize folic acid because of the biochemical structural similarity of their pyrimidine and hydantoin rings to the pterodyl portion of folic acid [*12*]. However, the addition of these agents to certain microbiological systems has provided no evidence of inhibition of folic acid metabolism. For example, primidone had no influence on microbiological assays for folic acid and vitamin B_{12} [*19*]. Broquist added Dilantin to culture media containing Strep. fecalis and varying concentrations of folinic acid [*46*]. No inhibition of growth was noted. Furthermore, the addition of primidone and phenobarbital to urine did not interfere with microbiological assay for folic acid [*12*]. It is of incidental interest that phenobarbital enhanced rather than suppressed the growth-producing effect of small amounts of vitamin B_{12} in cultures of Lactobacillus leichmannii [*47*].

On the other hand, clinical experience strongly supports the concept that these drugs are etiologic in the megaloblastic disorder. Temporary remissions have been obtained following withdrawal of Dilantin [*2,15*]. In another case withdrawal of primidone resulted in a reticulocytosis of 16 per cent and gradual correction of the anemia [*19*]. In three instances following response to folic acid therapy, this agent was discontinued and anticonvulsant drugs were reintroduced [*8,11*]. Relapses occurred within four to eight months.

Although inhibition of folic acid metabolism by anticonvulsant drugs could not be demonstrated in microorganisms, there is evidence to suggest that such interference is operative in man. Hawkins and Meynell noted slight but significant macrocytosis (without anemia) in about one-third of a group of patients receiving Dilantin and/or phenobarbital and suggested that this finding was an index of a disturbance in nucleoprotein metabolism [*27*]. The macrocytosis was readily corrected by the administration of folic acid but not by vitamin B_{12}. In two cases withdrawal of the anticonvulsant drugs alone brought about disappearance of the macrocytosis. The dramatic response of our patient (Case 1) to a much smaller amount of folic acid than previously employed also suggests that further studies should be carried out regarding the question of drug interference with folic acid metabolism. The experience with this patient likewise confirms previous observations that withdrawal of the anticonvulsant drugs is not necessary if folic acid treatment is instituted.

If the development of frank megaloblastic anemia were simply a matter of interference with folic acid metabolism by the anticonvulsant drugs [*27*], one would expect a much higher incidence of this disorder among epileptic subjects receiving these drugs. The conditioning features for the development of the clinical disorder remain unknown. Dietary deficiency may play a role. Unfortunately, in the majority of cases no mention is made of the dietary status. Dietary inadequacy was a prominent feature in thirteen cases [*2,16–19,24,28–30*]. The diet was briefly described as adequate in ten cases [*3–5,7,8,12,13,20*]. In certain cases (e.g., our Case 1) the multiple nutritional deficiency may superficially appear mild, no one particular facet being clinically marked. In the absence of thorough dietary history and nutritional studies, such could be overlooked. A poor dietary history in some epileptic patients is not surprising. Those with disease severe enough to require institutionalization or those with permanent, incapacitating neurological damage (e.g., our Case 11) or mental deterioration may be in-

capable of choosing or may not desire adequate nutrition. In five of the ten cases in which the diet was briefly described as adequate, the patients were mentally defective or psychotic [*5,7,13,20*]. In all, sixteen of the total fifty-eight patients were described as mentally defective or psychotic.

Regardless of the etiology of anticonvulsant megaloblastic anemia, some folic acid disturbance seems to play the dominant role. Seventeen patients have responded to folic acid therapy alone [*2,8,9,11,16,19,21,24,25,27,29,30*], fourteen to vitamin B_{12} alone [*1,2,6,8,10,14–17,26,27*] and five to combined therapy with these two agents [*8,21,25,28*]. Twelve patients failed to respond to vitamin B_{12} therapy but remitted promptly with folic acid [*3–5,7,12,13,15,18,26*]. In no instance was there a valid treatment failure with folic acid.

The dominant role played by folic acid seems further substantiated by the rapid clinical and hematological response of our patient (Case I) to the ingestion of 500 μg. of the vitamin daily, accompanied by a fall in urinary formiminoglutamic acid excretion. (Fig. 1.) Formiminoglutamic acid is an intermediate in histidine metabolism. The formimino group normally is transferred to tetrahydrofolic acid. In folic acid deficiency states the formimino group is not thus removed, and this compound is excreted intact in the urine [*45*].

Despite dietary and biochemical evidence of vitamin C deficiency, at no time did our two patients present clinical manifestations of scurvy. Vitamin C deficiency has been considered to play an adjuvant role in certain megaloblastic states in infants and adults [*48,49*]. Ascorbic acid has been thought to be concerned with the conversion of folic to folinic acid [*48,50,51*]. A low fasting serum ascorbic acid concentration was reported in one patient [*27*]. In another patient the vitamin C saturation test was normal [*3*]. In three patients this test gave subnormal values initially [*4,17*], but in two of these values subsequently became normal following the ingestion of larger amounts of vitamin C. In four patients, treatment with ascorbic acid did not improve the megaloblastic anemia [*17,18,27*] although in two, cutaneous purpura was benefited [*17,18*]. Purpura in anticonvulsant megaloblastic anemia cannot necessarily be ascribed to vitamin C deficiency since in some patients with this manifestation, thrombocytopenia was present [*6,16,18,27*].

The low serum vitamin B_{12} concentration in our patient (Case I) lacks complete explanation since the available dietary history did not suggest extreme deficiency in sources of this vitamin. The normal Schilling test and the absence of histamine achlorhydria and neurological findings of combined system disease exclude Addisonian pernicious anemia. In anticonvulsant megaloblastic anemia serum vitamin B_{12} concentrations have usually been normal or at least greater than 100 μμg. per 100 ml. [*2,4,5,12,13,17,27–29*]. In three patients the concentrations were distinctly low with values of 45, 40, and 85 μμg. per 100 ml., respectively [*18,27*].

Vitamin B_{12} absorption was normal in all eleven patients studied [*2,4,10,13,18,26–30*]. Free hydrochloride was present in all but four [*1,2,10,14*] of the thirty-nine patients tested. Vitamin B_{12} absorption was tested and found to be normal in two of these patients [*2,10*].

There has been no evidence of significant malabsorption in patients with anticonvulsant megaloblastic anemia. Diarrhea was described in only two patients [*16,29*] and was not a prominent feature in either. Steatorrhea has not been described and was emphatically disclaimed in many of the reports. In our patient (Case I) normal oral glucose, d-xylose and folic acid tolerance tests and normal stool fat provide evidence against any significant absorptive defect. The oral glucose tolerance test was normal in all but two [*14,17*] of the fourteen patients tested. Tests of folic acid absorption were normal in the seven patients studied [*12,13,27*]. Some studies to assess fat absorption were carried out in twenty-three patients [*2–9,11,14,16,18,24,26,28,29*]. In nineteen patients (including five in whom fat balance studies were specifically stated as carried out over periods of four to twelve days) the results were definitely normal. In one study using I^{131}-labelled fat, fat absorption was normal [*29*]. In the remaining four patients the data are difficult to evaluate. In one, the result of "58 per cent absorption" on a three-day fat balance study was considered unreliable by the authors [*5*], and in three the fecal fat contents were simply listed as 23, 28, and 38 per cent (dry weight), respectively [*6,7,17*].

In twenty-two patients studied, liver function tests were essentially normal. Some degree of iron deficiency due to blood loss probably complicated the condition in our patient (Case II), but this did not appear to be of importance since it did not interfere with the response to folic acid.

There is precedent for the production of megaloblastic type of anemia by a combination of factors, i.e., dietary deficiency and drugs. Cartwright and his associates produced an experimental porcine anemia which was characterized by the presence of some "atypical" megaloblasts in the bone marrow [*52*]. The multiple factors necessary to produce and maintain this disorder included omission of folic acid and vitamin B_{12} from the diet, the use of antibacterial agents to reduce the gut flora, and the administration of an antifolic drug. Despite the complex conditions necessary to produce this disorder, administration of folic acid alone gave hematological remission even though this was only temporary. The experience with anticonvulsant megaloblastic anemia appears similar except that the benefit from folic acid seems more lasting.

The fever, abdominal pain, mild arthritis and splenomegaly present in Case 1 deserve comment. The presence of fever in some cases of pernicious anemia and its prompt disappearance with therapy have recently been re-emphasized [*53*]. Fever has been noted in other cases of anticonvulsant megaloblastic anemia [*8,17,20,21*]. This manifestation disappeared promptly on the fourth day of treatment in Case 1 and did not recur. Abdominal pain has been described as a complication of Dilantin therapy [*51*]. With respect to the arthritis, it is of interest that the Coombs' test was positive in two patients with anticonvulsant megaloblastic anemia [*4,17*] and that disseminated lupus erythematosus has been described in association with another hydantoin antiepileptic, mesantoin [*55*]. Both the Coombs' and L.E. cell tests were repeatedly normal in our Case 1. Splenomegaly was described in four cases of anticonvulsant megaloblastic anemia [*13,27,28*].

The minimal daily requirement of folic acid in man has not been established. Chung and her associates have suggested, after analyses of diets of a "healthy population," that the daily folic acid intake of the normal American adult is probably not more than 200 μg. [*56*]. Chung also stated that such an intake is probably more than adequate since the diets analyzed were luxurious by current standards. The striking response of our patient (Case 1) to the ingestion of only 500 μg. of folic acid per day fits the concept that daily requirements in the normal adult are of this order of magnitude.

SUMMARY AND CONCLUSIONS

Two cases of megaloblastic anemia associated with the use of Dilantin and barbiturates are presented. Detailed nutritional studies indicated poor dietary habits and in particular low intakes of folic acid, vitamins C and B_{12}, and carotene. Urinary formiminoglutamic acid excretion provided further evidence of a folic acid deficiency state in the patient (Case 1) studied. This patient experienced complete clinical and hematological remission with the ingestion of 500 μg. of folic acid daily. Further studies demonstrated no evidence of a malabsorption defect or Addisonian pernicious anemia.

To date no inhibition of folic acid has been demonstrated when anticonvulsant drugs were added to certain microbiological systems. However, the clinical experience obtained with remissions, following withdrawal of anticonvulsant drugs and relapses upon re-institution of these drugs, leaves little doubt that these agents are concerned with the development of the megaloblastic anemia. The reported occurrence of macrocytosis without anemia in a large proportion of epileptic patients receiving these anticonvulsant drugs further supports this conclusion.

A frequent conditioning feature for the development of anticonvulsant megaloblastic anemia may be the presence of occult nutritional deficiency secondary to an inadequate diet. Some folic acid deficiency state seems paramount. Vitamin C deficiency may play a role in some cases since the dietary sources of ascorbic and folic acids are virtually identical. Mild to moderate vitamin B_{12} deficiency, when present, may augment the megaloblastic disorder but does not appear to be necessary or even frequent. The deficiency in carotene in our patients probably reflects the dietary inadequacy without influencing the megaloblastic picture.

Whether nutritional deficiency is actually a prerequisite for the development of the megaloblastic anemia remains unsettled. However, the demonstration of some dietary deficiency in many of the well investigated cases and the rarity of frank megaloblastic anemia among the multitude of epileptic patients receiving these anticonvulsant drugs, suggest that malnutrition frequently plays a role.

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ADDENDUM

We have recently become aware of two additional cases reported in the literature [*57,58*].

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Review

Factors Which Influence the Radioactive Iodine Thyroidal Uptake Test*

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THE measurement of the ability of the thyroid gland to accumulate radioactive iodine has become an established diagnostic procedure [*10,126*]. Despite the apparent simplicity of the test, the dynamics of normal iodine metabolism are complicated and the number of factors which can influence the observed results are legion. It is the purpose of this review to compile and evaluate the information concerning the substances and conditions which interfere with the use of this test as an indication of thyroid hormone production.

I^{131} has been used to diagnose thyroid disease in many different ways. The uptake in the thyroid has been measured at various intervals from one to forty-eight hours. The thyroid iodine clearance, the thyroid accumulation rate, the thyroid accumulation gradient, the I^{131} conversion ratio, the I^{131} urinary excretion, and the various thyroid scanning procedures have also been used. Some of these procedures have specific value in the study of thyroid function but the twenty-four-hour uptake has been the standard test in most medical centers and the discussion in this paper will largely be confined to this test. When clinical observations have been inadequate to permit any generalizations, pertinent animal or *in vitro* experiments with possible clinical implications are cited.

NORMAL VALUES

The normal values for the twenty-four-hour radioiodine thyroidal uptake test are generally considered to be as follows: Low, 0 to 15 per cent; normal, 15 to 45 per cent; high, 45 to 100 per cent.

An exact statistical expression of normal values is not possible because of the difference in measuring technics and because of the difference of frequency distribution and range of "normal" uptakes in different geographic areas. Cassidy and Vanderlaan [*25*], for example, compared the radioactive iodine uptake values of ninety-one normal persons in Boston, Massachusetts, and 125 euthyroid people in La Jolla, California, and found that 39.2 per cent of the subjects in La Jolla had uptake values below 20 per cent whereas in Boston only 9.9 per cent of the subjects had values below 20 per cent.

In a survey of 2,477 tests Werner [*127*] found the range of normality for the twenty-four-hour I^{131} uptake to be 15 to 45 per cent. About 16 per cent of all patients had uptake values in the region between 40 and 54 per cent. Virtually no normal persons had values in excess of 55 per cent or below 9 per cent. In 385 cases of hyperthyroidism, values were less than 45 per cent in 14 per cent, but none was less than 40 per cent. In hypothyroidism, the number of patients was small but the overlap into the normal range seemed to be of the same order of magnitude.

GENERAL PATHWAYS OF IODINE METABOLISM

The drugs and toxic substances which affect iodine metabolism usually act at discrete sites in the steps involved in the formation and release of the thyroid hormones. A detailed description of hormonogenesis is beyond the scope of this review but Figure 1, modified from the excellent review of Berson [*11*], schematically presents the prevailing concepts and provides a scheme of reference when the actions of antithyroid substances are specifically considered. Tables I through III provide summaries of factors which influence I^{131} uptake. Table IV lists factors which do not influence I^{131} uptake.

It is helpful to consider thyroid iodine metabolism in three general categories: (1) *Iodide trap-*

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POSSIBLE SITES OF ACTION OF DRUGS AND FOODS ON THYROID IODINE METABOLISM

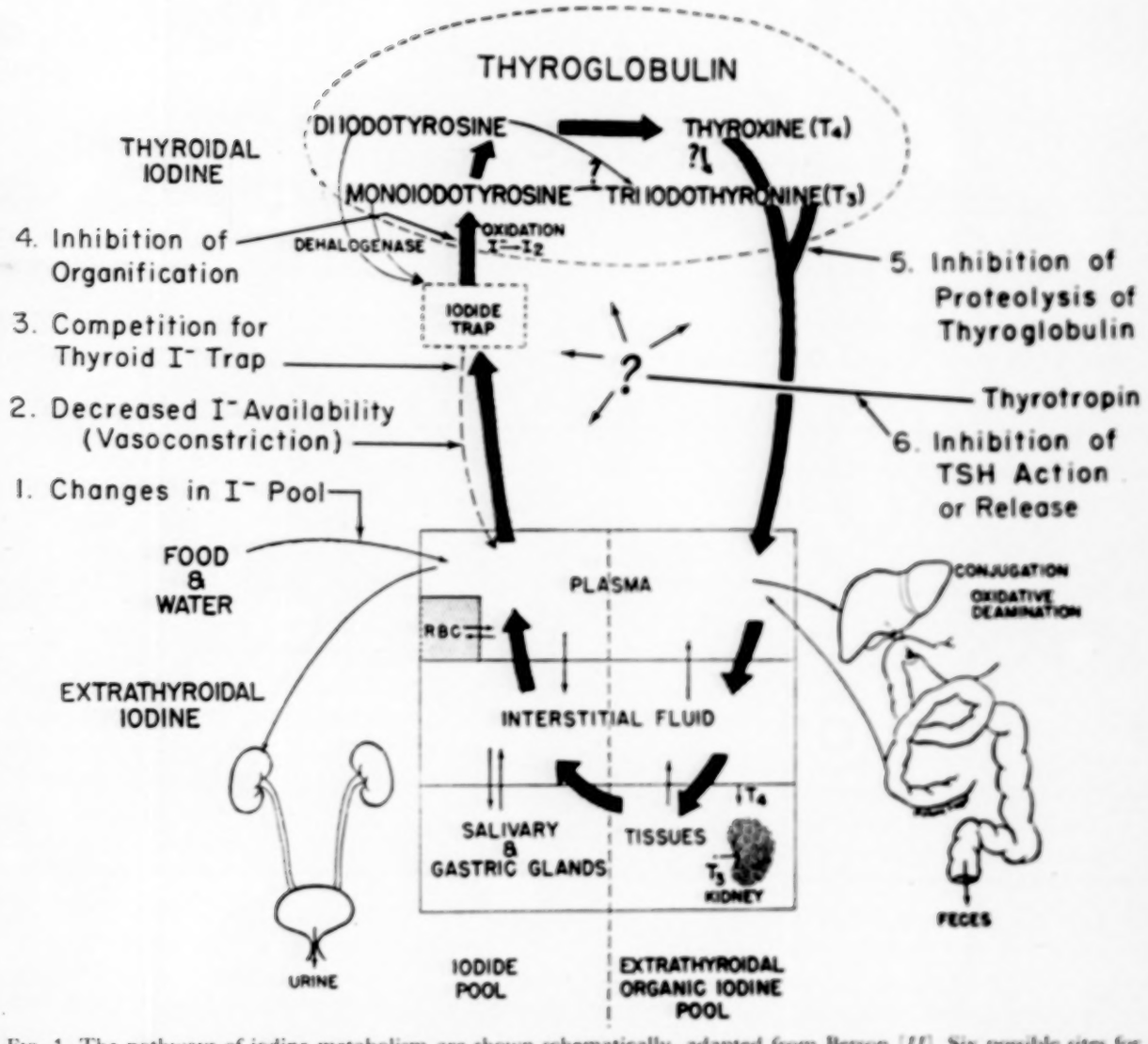


FIG. 1. The pathways of iodine metabolism are shown schematically, adapted from Berson [11]. Six possible sites for interference with normal thyroid metabolism are described which may cause variations in the thyroidal uptake of radioactive I^{131}. Examples of drugs which cause interference at these sites are: (1) Changes in size of iodine pool: *iodine;* (2) decrease in iodine availability: vasoconstriction induced by *epinephrine;* (3) competition for iodine trap: *potassium thiocyanate;* (4) interference with "organification": *thiouracil;* (5) changes in rate of proteolysis of thyroglobulin: *iodine;* and (6) change in rate of release or action of thyrotropin: *thyroid hormone.*

ping: Iodide is selectively concentrated within the thyroid cell to provide the substrate for subsequent steps. (2) *Hormonal synthesis:* The next series of reactions involves the activation of iodide by oxidation, with sequential iodination of tyrosine residues of thyroglobulin to form the mono- and diiodotyrosines. Conjugation of the iodotyrosines gives rise to thyroxin, 3, 5, 3′ triiodothyronine and traces of other iodothyronines. (3) *Hormonal release:* The iodinated amino acids are liberated from thyroglobulin by proteolytic enzyme(s) secreted by the thyroid cell. The iodotyrosines are selectively deiodinated within the thyroid follicular cell but thyroxin and triiodothyronine are spared and permitted to enter the blood stream.

TABLE I

FACTORS WHICH CAUSE LOW TWENTY-FOUR-HOUR I^{131} UPTAKE

- Excess iodine or iodide
  - Iodine medications (see Table V)
  - Diet
    - Foods (see Table VI)
    - Iodized salt
  - Radiographic media
- Goitrogenic foods
  - Brassica family
    - Turnips
    - Cabbage
    - Kale
    - Rape
  - Milk from cattle eating chou-moullier and certain other fodders
- Thiourylene derivatives
  - Thouracil
  - Propylthiouracil
  - Methimazole
- Aromatic antithyroid drugs
  - Resorcinol
  - Aminobenzenes
    - Para-aminosalicylic acid
    - Para-aminobenzoic acid
  - Sulfonylureas
- Cardiac decompensation
- Sedatives
  - Thiopental
  - Bromides if contaminated with iodine
- Miscellaneous drugs
  - Monovalent anions
    - Perchlorate
    - Thiocyanate
    - Others, vitamin A, phenylbutazone, salicylates
- Hormones
  - Adrenocortical steroids
    - Endogenous steroids activated by adrenocorticotrophic hormone
    - Cortisone and related compounds
    - Desoxycorticosterone
  - Thyroid
  - Progesterone
  - Testosterone

TABLE II*

POTENTIAL CAUSES OF LOW I^{131} UPTAKE

- Heavy metal administration
  - Mercury
  - Cobalt
  - Arsenic
  - Bismuth
- Goitrogenic foods
  - Peach, pear, strawberry, spinach, carrot [*16*]
  - Peanuts
- Antibiotics
  - Penicillin
  - Chlortetracycline
  - Chloramphenicol
  - Sulfonamides
- Morphine
- Epinephrine

* Substances listed in this table are considered to be unconfirmed in man.

TABLE III

CLINICAL AND EXPERIMENTAL FACTORS WHICH MAY INCREASE I^{131} UPTAKE

- Iodine deficiency
- Chronic liver disease with dietary iodine deficiency
- Rebound phenomenon following withdrawal of antithyroid drugs
- Nephrosis
- Estrogens
- Low serum chlorides
- Soy bean meal, cellulose and bulk producers

TABLE IV

FACTORS WHICH APPARENTLY DO NOT INFLUENCE THE TWENTY-FOUR-HOUR THYROIDAL I^{131} UPTAKE

- Mercurial diuresis
- Malabsorption syndrome
- Increased glomerular filtration
- Decreased glomerular filtration
- Sedatives
  - Reserpine
  - Pentobarbital
  - Tribromoethanol

The thyroid gland is under the direct regulation of the anterior pituitary by means of thyrotropin and indirectly subject to hypothalamic control by mechanisms which remain largely undefined.

THE EFFECTS OF EXOGENOUS IODINE AND IODIDES

Normal Requirements. Before consideration of the important subject of exogenous iodine and iodides as a cause of decreased I^{131} thyroidal uptake, it is necessary to define the daily requirements and the average intakes of iodine prevalent in this country.

The recommended iodine intake for adults needed to satisfy physiologic requirements is 2 to 4 μg. grams per kg. of body weight per day [*3*]. No special requirements dependent on sex, physical activity, pregnancy or lactation are recognized. The mean daily normal thyroidal accumulation of iodine is about 75 μg. and the average daily urinary iodide excretion is about 150 μg. [*11*]. It is probable that an intake of 200 μg. in an adult weighing 70 kg. is optimal [*52*].

Actual Normal Daily Intake of Iodine. Iodized salt in the United States contains 0.01 per cent potassium iodide. If an adult takes 6.2 gm. of salt daily, calculated as the usual American salt intake, he therefore ingests 620 μg. of

potassium iodide, equivalent to 474 μg. of iodine. According to Beierwaltes [*10*], the average person living in Michigan and using iodized salt ingests a total of 600 to 800 μg. of iodine a day. Ralls [*83*] estimated the dietary intake of iodine of eight normal persons on an ordinary diet, living in the New York area, to be about 126 μg. a day.

What is Iodine Excess? Intake of iodine in excess of the values quoted will eventually lower the thyroidal I^{131} uptake of a person. The amount of iodine necessary to depress radioactive iodine uptake has been determined in the case of hyperthyroidism [*42*]. One milligram of iodide daily for four days appeared to be the minimal effective dose that will inhibit the thyroid accumulation rate. This value, of course, might not be applicable to euthyroid people.

In acute experiments in which stable iodide was added as a carrier to I^{131} and administered to iodine-deficient people, the proportion of the radioactive dose that was accumulated by the thyroid was independent of total iodine below 1.5 mg., but when larger amounts were given progressively smaller fractions of the radioactive dose were accumulated [*114*].

THE MECHANISMS WHEREBY EXOGENOUS IODINE REDUCES THE THYROIDAL UPTAKE

Iodide Dilution. Iodide added to the total body iodide pool causes a decrease in the thyroidal I^{131} uptake by lowering the specific activity of body iodide. The uptake of the radioiodine by the thyroid gland does not indicate the gravimetric amount of iodine trapped, but simply represents the percentage of the total stable iodide pool trapped in the same period of time [*5,101*]. Thus an enlarged iodide pool due to added iodide results in a lower uptake, and a contracted pool due to iodine deficiency causes an increased uptake of I^{131} [*40*].

Inhibition of Thyroxin Output. In addition to the dilutional effect of iodide upon the radioactive test, iodide inhibits thyroid hormone synthesis and release under certain circumstances. This effect of iodide, of course, has been used therapeutically for a long time in the treatment of hyperthyroidism. Means [*73*] found that the smallest daily dose of iodine which, with any certainty, will produce a maximum inhibition of the basal metabolic rate in thyrotoxic people is 6 mg.

Some of the theories concerning the antithyroid action of iodide follow:

(1) By interfering with the iodination mechanism of tyrosine necessary to form the precursors of tri-iodothyronine and thyroxine [*79,99,115, 121*]. Two suggested mechanisms for this are: (a) Decrease in the effective concentration of hypoiodous acid, a postulated active form of iodide [*98*] and (b) trapping of available elemental iodine, I_2, in the inactive form of I_3 [*36,98*].

(2) By chemical action on the thyrotropic hormone at some point after its release from the pituitary gland [*42*]. Some support for this view is found in the *in vitro* inactivation of thyrotropin by iodine [*2*]. It is possible, however, that thyrotropic hormone is not involved in thyrotoxicosis [*35,128*].

(3) Inactivation of proteolytic thyroid enzyme(s) which releases thyroxine from thyroglobulin [*31*].

Occasionally in a patient treated for prolonged periods of time with iodides, in bronchial asthma for example, myxedema and goiter will develop [*79,119,120*]. Radioiodine studies in such cases suggest that the hypothyroidism is due to failure of thyroid hormone synthesis. Inasmuch as in large numbers of asthmatic patients so treated thyroid abnormalities do not develop, it is possible that iodide goiter of this variety occurs only in predisposed subjects on the basis of an idiosyncrasy. In support of this concept is the report of Greer [*49*] that he was unable to detect any effect on the endogenous secretion rate of thyroid hormone by iodide in five euthyroid subjects.

For further details concerning the actions of iodide, the reader is referred to the excellent review by Vanderlaan and Storrie [*122*].

SOURCES OF EXCESS IODINE INTAKE

Exogenous iodine may come from drugs, iodized salt, foodstuffs and x-ray contrast media. Evaluation of all these sources of iodine should be routine in the interpretation of I^{131} thyroid uptake test results. Lugol's solution, for example, contains about 5 to 8 mg. of iodine per drop. Potassium iodide and other iodides are present in many commonly used medications [*86*]. (Table v.) Administration of these preparations, therefore, will produce lower thyroidal uptakes of radioactive iodine (RAI).

Vitamin Tablets and Iodized Salt. Kohn and Nichols [*62*] reported interference with the uptake of RAI during the administration of vitamin-mineral mixtures. Eight euthyroid persons were given Gevral,® which contains 0.5 mg.

TABLE V

IODINE IN DRUGS: A REPRESENTATIVE LIST

Preparation	Usual Dose of Drug	Amount of Available Iodine Daily (μg.)	Hypothetical Absorbed Daily Dose of Drug
Vitamin-Mineral			
Mi-cebrin® tablets	1 tablet daily	150	.....
Unicap® Therapeutic	1 tablet daily	150	.....
Gevral® capsules	1 capsule daily	500	.....
Gevrabon® liquid	1 ounce daily	100	.....
Expectorants			
Calcidin	1 to 3 gr. every ½ to 3 hours (15 per cent iodine)	24,000	1.6 gm.
Dainite-KI® tablets	4 tablets daily (320 mg. potassium iodide per tablet)	98,000	1,280 mg. of potassium iodide (77 per cent iodine)
Topical Agents			
Vioform® ointment, (iodochlorhydroxyquin) cream, suppositories (3 per cent Vioform)	.....	2,460	2 gm. of 3 per cent cream (100 per cent Vioform contains 41 per cent iodine)
Iodex® ointment, (4.7 per cent iodine)	Applied liberally to wounds	9,400	2 gm.
Floraquin® vaginal tablets (100 mg. diiodoquin per tablet; 7.5 per cent per ounce of powder)	2 tablets or 4 to 8 gm. of powder 3 to 7 times per week	38,400	8 gm. of powder
Miscellaneous Drugs			
Pathilon® (3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol-ethyl-iodide)	25 to 50 mg. 3 to 4 times daily	.....	.....
Diodoquin® (5,7-diiodo-8-hydroxyquinoline)	1 tablet (650 mg.) 3 times daily	128,000	2 gm. (64 per cent iodine)

of potassium iodide per capsule. In only three of these subjects was there a significant difference in the RAI uptake after daily administration, as compared with control values. In the first case the value was 37 per cent before medication and 13 per cent after medication. In the second case, the value was 35 per cent before medication and 24 per cent after medication. In the third case the value was 62 per cent before and 16 per cent after taking one capsule of Gevral daily for one week.

The evidence suggests, therefore, that the amount of iodide present in some vitamin-mineral tablets, administered once daily, is sufficient to lower significantly the I^{131} thyroidal uptake at twenty-four hours if the person is iodine-deficient.

If one compares these result with the RAI uptakes found in the patients described by Kelsey et al. [61] before and after the use of iodized salt in cooking, it will be observed that the results are similar. Fifty-four inmates of a mental institution, who had been receiving non-iodized table salt in their diet for a prolonged period of time, were studied. Before the use of iodized salt nineteen of these fifty-four patients had an RAI uptake of over 40 per cent. Of these nineteen patients, eighteen had normal protein-bound iodine values and normal radioactive protein-

TABLE VI
IODINE CONTENT OF FRESH, UNCOOKED FOODSTUFFS
[3,17,47]

Food	Iodine Content (μg./kg. of edible portion of food)	Weight of Average Serving (gm.)	Iodine Content of Average Serving (μg.)
Banana	200	150	30
Cauliflower	1,200	60	72
Spinach	201	100	20.1
Sweet cherry	3,300	100	330
Sardines	284	50	14.2
Halibut	520	100	52
Herring	520	100	52
Cod	1,463	100	146.3
Cod liver oil	8,387	5	41.9
Haddock	3,180	100	318
Oysters	577	100	57.7
Lobster	1,020	100	102
Shrimp	1,300	100	130

bound iodine values in the blood. Twelve of these patients were tested again after iodized salt had been introduced into the cooking at this institution. The median RAI uptake before the use of iodized salt was 49 per cent and the median uptake after the use of iodized salt was 23 per cent. The conclusion reached by these authors was that the initial high values were due to iodine deficiency. The subsequent values, therefore, probably represented "normal" RAI uptakes.

Iodine in Foodstuffs. An excessive seafood diet has been said to provide enough dietary iodine to lower the thyroidal I^{131} uptake. There apparently have been no studies specifically performed to investigate this question. However, a brief review of the iodine content of certain foods particularly rich in iodine will serve as a reminder that the patient can obtain rather large amounts of this element from this diet. Foods which do not come from the sea, of course, may vary in their iodine content, depending on the iodine concentration of the soil in which they were produced. (Table VI.)

Iodides in X-Ray Contrast Media. Most of the contrast media which are used to demonstrate organs and other spaces radiographically contain large amounts of iodine. In some of these media, iodine is released from its organic binding as iodide, and swells the total body pool; this excess iodide decreases the radioactive iodine uptake by the thyroid.

Even barium sulfate used in gastrointestinal radiography has been incriminated (without documentation) as an inhibitor of the uptake test because of iodide present as an impurity [*10*]. Barium sulfate (U.S.P., for radiologic diagnosis) contains less than five parts of total iodide and iodine per million by weight [*70*]. About 200 gm. of barium sulfate powder used in the routine radiologic examination of the upper gastrointestinal tract would therefore provide less than 1 mg. of iodine per examination. Even if all the iodine were absorbed, this amount of barium sulfate in a single dose probably would not significantly affect the I^{131} thyroidal uptake.

The iodinated compounds used in cholecystography contain large concentrations of iodine (50 to 65 per cent), and despite the fact that these substances are usually excreted shortly after administration, there is a variable moiety which remains in the body for prolonged periods and is deiodinated before excretion, releasing iodide into the iodide pool.

Slingerland [*104*] found that the period of depressed thyroidal uptake of radioactive iodine following the administration of iodoalphionic acid (Priodax®) in the euthyroid subject was usually less than four weeks, and in the hyperthyroid patient, one week or less. There is, however, a wide variation in the response of subjects to the effect of Priodax. Newman and Cupp [*77*] have made similar observations in eleven euthyroid patients; the twenty-four-hour thyroidal uptake was reduced to less than 10 per cent in all of them during the first week after the administration of Priodax. In ten patients the uptake had become normal within thirty days; the other patient required forty-two days to return to normal.

Inhibition by iodinated compounds used for visualization of the gallbladder differs in duration, depending on the type of compound used. The I^{131} uptake in seventy-four subjects before and after the administration of iopanoic acid (Telepaque®) was markedly reduced for the first few days and was restored to within 30 to 40 per cent of control values at the end of one week [*27*]. The subsequent rate of recovery approximated 1 per cent per day. Restoration of the average was about 60 per cent complete at thirty days and about 90 per cent at sixty days. Iodipamide (Cholografin®) administered intravenously to seven euthyroid subjects de-

creased the uptake of I^{131} for an average of about three months [*91*].

The iodinated compounds used in intravenous pyelography may interfere with the RAI uptake for as long as one month [*10*]. The effects of substances such as iodized poppy seed oil (lipiodol) used in myelography and bronchography on the I^{131} uptake test have not been adequately studied, although it is known that in some cases the uptake may be useless as a diagnostic tool for thyroid function for as long as one or more years [*102*]. In one case [*16*] the uptake was still zero one year after a bronchogram had been performed with lipiodol.

Studies [*138*] suggest that the prolonged effects of lipiodol on parameters of thyroid function are not limited to the use of the substance in bronchography and myelography, but include oral administration as well. The material is absorbed and stored in an unknown site. There is a continual release of iodine in quantities sufficient to lower the thyroidal I^{131} uptake and elevate the concentration of serum protein-bound iodine.

The thyroidal I^{131} uptake was depressed for 445 days (the duration of the study) in four subjects who received 10 to 20 cc. lipiodol orally.

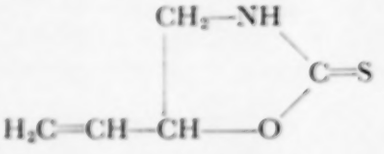
IODINE DEFICIENCY

Iodine deficiency increases the uptake of I^{131} by the thyroid to the range observed in hyperthyroidism. One hundred and three patients with goiter in the endemic goiter area of Mendoza, Argentina, were found by Stanbury and co-workers [*114*] to have a mean twenty-four-hour thyroidal uptake of 58.6 per cent. Well over half of the subjects tested had uptakes greater than 57.7 per cent. A similar group of patients living in the endemic goiter area of Bailadores in the Venezuelan Andes, where the diet is iodine-deficient, was studied by Roche and his group [*92*]. There were eighty-six adults with goiter who had an average forty-eight-hour thyroidal radioiodine uptake of 76 per cent of the dose administered; the uptake was 68 per cent in twenty four non-goitrous adults, and 79 per cent in twenty-eight children. The forty-eight-hour uptake values in seventy euthyroid adults in Caracas, the capital of Venezuela, by comparison, averaged 37 per cent and gave a frequency distribution curve similar to that found in Boston, Massachusetts.

In ten of twenty patients on the Kempner rice regimen, which is low in salt and undoubtedly also in iodine, uptakes increased to 46 per cent or more after three months on the diet [*13*].

GOITROGENIC FOODS

Certain foods eaten by man and animals are known to be goitrogenic because of chemical constituents which interfere with iodine metabolism. The precise mechanism of interference is as yet ill-defined, but appears to be at the level of "organification." Progoitrin is a thioglycoside present in many plants of the Brassica family, including cabbage, turnip, rutabaga, rape, kale and chou-moullier [*6,28,46, 130*]. The probable structure of goitrin isolated from yellow turnip and white turnip root and seed, and from the seed of cabbage, kale and rape, was determined by Astwood, Greer and Ettlinger in 1949 to be L-5-vinyl-2-thio-oxazolidone [*6*]:



This material is liberated from its glycoside complex by a thioglycosidase contained in the plant or seed itself. Cooking destroys this enzyme [*46*]. The consumption of raw vegetables of this class or of vegetables allowed to stand after mashing or freezing before cooking should be looked upon with suspicion in this regard. This chemical is equal in antithyroid potency to thiouracil [*45*]. The plants mentioned contain as much as 400 mg. of vinyl-thioxazolidone per kilogram of wet vegetable.

Recent studies [*137*] by Greer and Deeney indicate that, contrary to expectations, hydrolysis of progoitrin to goitrin occurs within the body in the absence of the exogenous thioglycosidase (myrosin). Progoitrin administered in a single daily dose of 1 gm. was found to be an effective agent in the treatment of thyrotoxicosis in one patient.

Chou-moullier, a forage plant for cattle, appears to be responsible for a significant amount of endemic goiter in Tasmania and Australia by providing a goitrogen which is transmitted in the milk. Clements and Wishart [*28*] injected extracts of chou-moullier into rats and noted a reduction of I^{131} uptake by 94 per cent. Goitrogens from other fodders may also be transmitted in milk.

Cabbage causes goiter in rabbits [*26*], but has not been demonstrated to be goitrogenic in man [*44*]. There are only two reports of goiter in human beings due to the ingestion of foods (other than the milk goiters in Australia and Tasmania): in one patient described by Fisher, Epstein and Pashkis [*39*] in 1952 a goiter (stroma cibaria) developed due to the excessive ingestion of rutabaga, turnips and cabbage. The twenty-four-hour radioactive iodine thyroidal uptake in this case was 8 per cent; seven months later, after removal of the foods in question from the diet, it was 19 per cent. Goiters are said to have developed in a group of Belgian monks in World War I who were forced to eat large amounts of rape seed and cabbage [*73*].

Arachidoside. A newly recognized glycoside, arachidoside, in the red skins of peanuts (groundnuts) causes goiters in rats [*112,113*]. The goitrogenic action of this substance is prevented by the administration of potassium iodide. There is no evidence that thiooxazolidones or cyanogenetic glycosides are present in the peanut. The twenty-four-hour I^{131} excretion in rats fed diets containing groundnut substances was increased, indicating a diminished thyroidal uptake. There are no reported studies on man.

Soy Beans. A new mechanism of goitrogenesis was suggested by Middlesworth [*74*] in a study of the action of soy meal in rats. He noted that soy meal is the only goitrogenic agent known, other than thyrotropic hormone, that produces a high twenty-four-hour radioiodine uptake. The fecal excretion of I^{131} after labeled thyroxine was given intraperitoneally was doubled in rats fed soy flour. Inasmuch as the total fecal mass was also twice that of control animals, the effects of adding cellulose and bran to the control diets were also studied. These substances also increased both fecal mass and labeled iodine excretion. Increased fecal excretion of labeled thyroxine in soya-fed animals has been confirmed [*9*]. It was shown that the increased excretion of labeled iodine was not dependent on increased biliary excretion.

The goitrogenicity of soy flour can be attributed to excessive fecal loss of organic iodine, which increases the requirement for thyroxine synthesis and increases iodine deficiency. It is unlikely that a similar mechanism can induce goiter in man because the relative amount of thyroxine entering the gut is much smaller in man than in the rat [*51,129*]. Studies of this problem in man will be of great interest.

Cyanogenetic Glycosides. The goitrogenic effect of cyanides released from cyanogenetic glycosides in the Brassica and in certain other plants has been suspected but never established [*8*]. Some cyanides probably can act directly on the thyroid gland [*96,105*]. Also, it is known that small amounts of cyanide are transformed by enzymatic action in the liver to thiocyanate [*109,116*]. The goitrogenic effect of potassium thiocyanate is well known [*84,86*]. Plant cyanides [*22,50*] have not yet been implicated in human disease, but cyanide fumes have been blamed for hypothyroidism and goiter following occupational exposure [*54*].

AROMATIC ANTITHYROID DRUGS

Many aromatic compounds with an electron-donating group on the ring can inhibit synthesis of thyroid hormone [*36*]. These chemicals include the sulfonamides, the aminobenzenes and resorcinol. Both a free aromatic amine and a free aromatic hydroxyl group are present in the aminobenzenes and have been related to the antithyroid action of these drugs [*116,117*]. These substances may act by binding active iodine formed in the thyroid gland.

Sulfonamides. Most of the sulfonamide drugs are weak goitrogens in animals [*117*]. Neither goitrogenicity nor inhibition of thyroidal I^{131} uptake in man has been demonstrated. Sulfanilamide [*122*] in thyroid tissue slices suppresses the formation of thyroxin and diiodotyrosine almost completely, but the iodide-concentrating capacity remains unaltered. In an experiment in which 2 per cent sulfaguanidine was added to the diet of rats the average weight of the thyroid increased 150 per cent in two weeks [*69*].

Sulfonylureas. Both tolbutamide (Orinase®) and carbutamide possess antithyroid activity in the dose range used in the treatment of diabetes [*19*]. Carbutamide was found to be thirteen times as potent an antithyroid agent in the rat as sulfaguanidine and 1/200th as potent as propylthiouracil. The goiters produced by carbutamide were inhibited by excess iodide [*26*]. Six of nine patients in an acute study [*19*] had a decrease in the twenty-four-hour I^{131} uptake of more than 20 per cent of the control values with carbutamide, and four of the same nine patients when later tested with tolbutamide had a similar 20 per cent decrease. Although carbutamide suppressed the I^{131} uptake little or not at all in some cases, there was a rise in the uptake far above the initial level when the drug was discontinued. It ap-

peared that, in general, carbutamide is twice as potent an antithyroid agent as tolbutamide.

Para-aminosalicylic Acid (PAS). Balint, Fraser and Hanno [7] in 1954 reviewed nine cases of hypothyroidism associated with goiter in tuberculous patients undergoing therapy with PAS. Sutherland [116] studied five patients who were receiving 12 gm. of PAS daily and found that the mean I^{131} uptake at twenty-four-hours was reduced from 20 per cent before therapy to 14 per cent after one week of PAS therapy. In three patients receiving PAS for twenty-one to thirty days the mean radioiodine uptake was reduced from 31 per cent to 15 per cent. After the medication was stopped there was an increase in the uptake for three to ten days. Administering 10.5 gm. of PAS intravenously caused complete cessation of I^{131} uptake for a period up to fifteen hours [55].

Para-aminobenzoic Acid (PABA). Rats fed 2 per cent PABA in their diet had a 60 per cent increase in thyroid weights as compared to control rats. However, when a similar group of rats was also fed 1 mg. of sodium iodide per 100 gm. of diet, the goitrogenic effect of the PABA was completely nullified [69].

Resorcinol. Three cases of myxedema with goiter have been reported in patients treated with resorcinol ointments for leg ulcers [21]. In each the urinary excretion of radioiodine was below 10 per cent in forty-eight hours. These excretion rates, however, were all performed more than three days after the use of resorcinol ointment had been discontinued and probably represent the hyperavidity of the thyroid gland which has just been released from inhibitory effects of an antithyroid drug.

Doniach and Frazer [32] injected resorcinol into rats prior to administration of radioactive iodine tracer and found the thyroid iodine uptake 10 to 20 per cent of that found in control rats; this was comparable to the maximal reduction in uptake caused by thiouracil under similar experimental conditions. When the resorcinol was administered orally instead of parenterally there was a smaller but still definite antithyroid effect. Rosenberg [91] also confirmed the decrease in I^{131} thyroidal uptake in rats given resorcinol.

SEDATIVES

Many sedatives ameliorate to some extent the symptoms of thyrotoxicosis; therefore, it is important to determine whether or not they influence iodine metabolism in such a way as to affect I^{131} uptake. Wase, Repplinger and Foster [125] studied I^{131} uptake in rats and found that the administration of thiopental reduced thyroidal uptake of iodine in rats by 82 to 89 per cent. They found no effect with pentobarbital (Nembutal®), vinbarbital (Delvinal®) or tribromoethanol (Avertin®) therapy. The administration of reserpine also has been shown to be without significant effects on I^{131} uptake in thyrotoxicosis [24].

Findings in a series of thirty-one euthyroid and twelve hyperthyroid patients [139] indicate that the administration of promazine, meprobamate, hydroxyzine, or reserpine in the usual therapeutic doses for a period of ten to twenty-one days does not alter the thyroidal I^{131} uptake or the serum levels of cholesterol and protein-bound iodine in euthyroid or hyperthyroid patients.

Meprobamate. Yohalem [135] in a study of the effect of meprobamate (Equanil,® Miltown®) in ten patients with hyperthyroidism found that, despite the symptomatic improvement provided by 400 mg. of the drug taken four times a day, the radioiodine uptake test was not altered. A different conclusion regarding the effect of meprobamate on I^{131} uptake was reached by Friedell [38] who did a double blind study on twelve euthyroid people, using a placebo in one group, meprobamate 400 mg. three times a day in the second, and meprobamate plus 0.5 mg. of benactyzine hydrochloride (2-diethyl-aminoethyl-benzilate (Suavitil®)) three times daily in the third series. The average initial twenty-four-hour uptake was 49 per cent. After the placebo therapy, it was 44 per cent; after meprobamate therapy for three weeks, it was 33 per cent; and after the combination of meprobamate and benactyzine therapy, the average uptake was 28 per cent (in seven patients). The range of values initially was from 35 to 62 per cent and in the last group mentioned, the range was from 9 to 38 per cent.

Morphine. Data concerning the effects of the administration of morphine in man are not available. Chronic administration of morphine reduced the thyroidal iodine uptake in rats (two weeks of a daily dose of 2 mg.) approximately 50 per cent [95]. The thyroid weights were the same as in the control groups. Histological findings and simultaneous protein-bound I^{131} suggest that morphine interfered with the release of thyroid-stimulating hormone of the

anterior pituitary in some manner. The effects of morphine on iodine metabolism need to be determined in the presence and absence of addiction in man.

Bromides. Bromides are included in the list of inhibitors of RAI uptake not because bromide itself is an inhibitor but because some preparations of bromides may be contaminated with iodine. The bromide ion itself does not interfere with the enzyme systems for iodinating tyrosine [*134*].

Williams and co-workers [*132,133*] administered sodium bromide to rats and found that the thyroid uptake of I^{131} was not affected but an increased rate of excretion of the isotope in the urine occurred. Sodium bromide, 3 gm. daily, given to five patients for four weeks with substandard doses of thiouracil did not cause discernible potentiation of the antithyroid effect of the latter. Sixteen patients tested with radioiodine were given no carrier iodide, but received 2 gm. of sodium bromide. No difference was observed in the response of these patients and the ones given no carrier. No thyroidal I^{131} uptakes were determined however.

Therefore, it seems clear that the bromide ion by itself does not interfere with the collection of iodine by the thyroid.

MISCELLANEOUS DRUGS

A large group of unrelated chemicals which affect I^{131} metabolism have been studied. Some of these have been investigated only in the laboratory, however, and it may be that the effects in man differ.

Heavy metals, including arsenic, copper, lead, mercury, silver and zinc, have been found to interfere with iodine uptake *in vitro* by thyroid slices [*105*]. Inhibition of thyroid function *in vivo* has not been similarly produced but the possible effects should be investigated.

The monovalent anions investigated by Wyngaarden and his group [*134*] were shown *in vitro* to inhibit the iodide concentrating mechanism (iodide trap) of the thyroid gland. These substances included perchlorate, chlorate, iodate, bi-iodate, hypochlorite, periodate and nitrate. The action of these compounds was similar to that of thiocyanate.

It is of interest to note that *perchlorate* was ten times as potent and nitrate 1/30th as potent as thiocyanate in causing release of iodide previously collected by the thyroid. The mechanism of action is that of competition with iodide ion for the thyroid iodide concentration mechanism, just as it is for thiocyanate. Potassium perchlorate has been used successfully in the therapy of hyperthyroidism in both adults and children [*75,106*]. Godley and Stanbury [*41*] in 1954 found that the administration of 600 mg. daily of potassium perchlorate to thirteen hyperthyroid patients lowered the twenty-four-hour RAI thyroidal uptake markedly within two weeks after medication was begun. The mean control uptake was 77.5 per cent, with a range from 60.7 to 108 per cent. The mean uptake during perchlorate therapy was 15.9 per cent, with a range from 3.4 to 38.8 per cent. Only three uptakes were above 20 per cent.

Thiocyanate, a monovalent anion, was of more clinical importance in the past when it was used widely as an antihypertensive agent. In nine of fifteen cases of myxedema resulting from the use of thiocyanate [*15*] it was found that the twenty-four-hour I^{131} uptake was less than 10 per cent during the period of high thiocyanate blood levels. Withdrawal of the potassium thiocyanate medication from these patients resulted in a prompt subsidence of myxedema, disappearance of goiter when present, and a marked although temporary increase in the twenty-four-hour thyroidal I^{131} uptake. In seven cases the uptake rose to above 45 per cent of the ingested dose of radioiodine.

Cobalt has been implicated in the production of hypothyroidism with goiter [*63,89*]. Little [*67*], for example, reported five cases of goiter in children receiving a cobalt and iron preparation for anemia. In only one was the I^{131} uptake studied. The twenty-four-hour thyroidal uptake was 44 per cent five days after withdrawal of the drug and 17 per cent six months later. The value recorded initially perhaps represented a rebound phenomenon.

Roche and Layrisse [*93*] measured the twenty-four-hour thyroidal uptake of I^{131} in twelve adult euthyroid subjects receiving cobalt. Within a week after starting administration of cobaltous chloride in a uniform dosage of 50 mg. given orally three times daily the thyroid uptake in most cases was greatly reduced and by the second week was near zero; the values rose toward normal after cobalt was discontinued. These authors subsequently treated two patients with hyperthyroidism with cobaltous chloride successfully prior to thyroidectomy.

There is some dispute about the effects of cobalt, however. Jaimet and Thode [*58*] found

no significant change in thyroid function (thyroid I^{131} uptake, conversion ratio and salivary radioactivity) in fifteen children treated with cobaltous chloride in a dosage up to 6 mg. per kg. per day in the form of a cobalt-iron preparation for ten weeks; two other children showed a lowered thyroidal uptake after one course of cobalt but no effect following a second course. Scott and Reilly [*97*] found no difference in the thyroidal uptake of rats treated with cobaltous chloride in a dosage of 60 mg. per day, as compared to control rats.

Eight patients were treated for hyperthyroidism with cobaltous chloride and improvement in both clinical and laboratory parameters occurred in five [*82*]. The twenty-four-hour I^{131} uptake was lowered by a daily dose of 300 mg. of the drug from hyperthyroid levels to values ranging from 17 per cent of the administered dose down to zero in four subjects. This is convincing evidence that cobalt interferes with uptake and "organification" of iodine.

Phenylbutazone (Butazolidin®) was shown to cause marked depression of the radioactive iodine uptake by Linsk et al. in a study of thirteen patients [*66*]. The twenty-four-hour uptake was measured before and after four days of therapy (800 mg. per day). Uptake varied between 20 and 54 per cent before administration of phenylbutazone and between 5 and 13 per cent after administration of the drug.

Thiouracil Drugs. It is common knowledge that drugs such as thiouracil, propylthiouracil and methimazole depress the twenty-four-hour I^{131} uptake test values. What is less commonly known is the fact that after withdrawal of these drugs there is a period of high RAI uptake, which persists for approximately five days beginning with the second day of withdrawal. For a day or two after the rebound there may be a second low uptake phase before the normal level is regained [*10*]. It would seem wise, then, not to attempt the radioiodine test for a period of at least one week following withdrawal of antithyroid drugs of this class.

Vitamin A. For an as yet unexplained reason, vitamin A depresses the I^{131} uptake. Logan [*68*] tested the effect of the oral administration of 50,000 I. U. of vitamin A acetate daily for twenty-one to seventy-seven days in seven people. The twenty-four-hour uptake before treatment ranged from 21 to 68 per cent and the values after treatment ranged from 14 to 32 per cent. *In vitro*, however, vitamin A at 1×10^{-3} M concentration had no effect on the I^{131} uptake [*105*].

Salicylates. Brief and protracted administration of sodium salicylate in doses up to 9 gm. daily in human subjects produced decreased thyroid function as measured by serum protein-bound iodine levels and radioactive iodine thyroid uptake. The mean reduction in the twenty-four-hour uptake of I^{131} was 43 per cent of the control value in patients who had received 6 to 8.1 gm. of salicylate for eight to fifteen weeks [*4*].

HORMONES

The interrelated functions of the endocrine system are well exemplified by the effects that other hormones have upon the uptake of iodine by the thyroid gland. Hormones that have been studied in this regard include adrenocorticotropic hormone (ACTH), cortisone, epinephrine, desiccated thyroid, thyroxine, triiodothyronine, estrogen, progesterone, desoxycorticosterone, testosterone, and the obvious one, thyrotropin (TSH) [*14*].

ACTH and cortisone decrease the radioiodine thyroidal uptake. Eighteen of twenty-four patients observed by Berson and Yalow [*12*] had an 8 to 34 per cent decrease in the twenty-four-hour I^{131} uptake between the fifth and eleventh days of therapy with doses of 100 to 300 mg. of cortisone daily. Berson [*11*] concluded that, even though the renal clearance of I^{131} was frequently increased during cortisone therapy, the decreased thyroidal uptake was not to be explained on this basis since thyroidal clearances were markedly depressed, frequently to hypothyroid levels.

Although the major effect of corticosteroids might be to suppress TSH formation, Epstein and his group [*34*] provide evidence of a direct action of corticosterone on the thyroid. They administered ACTH and cortisone to groups of hypophysectomized rats and found that there was significant inhibition of the thyroidal I^{131} uptake which had been induced previously by exogenous thyrotropin.

Epinephrine. Epinephrine increased the four hour I^{131} thyroidal uptake in five euthyroid subjects tested by Reiss, Forsham and Thorn [*88*]. This finding has not been confirmed or explained. Patients with Addison's disease studied the same way showed no change in radioiodine uptake. However, the injection of epinephrine into the intact rat results in a

decrease of the thyroidal uptake of I^{131} of from 45 to 67 per cent as compared with control animals [*107*]. This was in sharp contrast to the results obtained in similarly treated adrenalectomized rats in which there was an increase in the I^{131} uptake of 27 to 56 per cent over that of the control animals.

The work of Brown-Grant and Gibson [*18*] on the effect of exogenous and endogenous epinephrine on the radioiodine uptake in the rabbit may have important clinical implications, particularly in regard to non-specific stress in man. These workers administered epinephrine intravenously to rabbits, both conscious and anesthetized, at a slow rate so that there was no demonstrable rise in the blood pressure. With 2 to 4 μg. of epinephrine per minute, there was intense vasoconstriction of the thyroid blood vessels which apparently caused complete inhibition of the I^{131} thyroidal uptake (measured up to four hours after the intravenous administration of the tracer iodine). The action of Adrenalin® was proved to be unrelated to thyrotropin in these animals; in nine experiments TSH was injected after the administration of Adrenalin was begun and in no instance was any increase in the rate of uptake observed. Other authors have commented on the inhibitory effect of "stress" in animals, including the "emotional" stress of restraint [*124,131*]. This interesting finding should be considered in evaluating not only the design of radioactive iodine tests, but also the test results in man.

In contrast to the effect of epinephrine on I^{131} uptake by the thyroid gland is the related finding by Ackerman [*1*] that the thyroid vein blood in dogs contained increases in protein-bound radioiodine levels of from 1.5 to 17.1 times control values within ninety-five minutes after the intravenous administration of epinephrine or norepinephrine.

The Effects of Thyroid Hormone. During the administration of desiccated thyroid, thyroxin and triiodothyronine, the radioiodine uptake of normal subjects is suppressed [*30*] because of inhibition of the release of thyroid-stimulating hormone by the anterior pituitary. This inhibition is not evident in most patients with Graves' disease [*10*]. The return of normal iodine metabolism following discontinuance of these medications has been investigated by Greer [*48*] in forty-seven normal human subjects. Depression of the RAI uptake to below 10 per cent was noted in ten of eleven subjects after they had received 3 gr. of desiccated thyroid daily for eight days. In one-third of twenty-five subjects depression of the RAI uptake to below 10 per cent was noted after the administration of only 1 gr. of desiccated thyroid daily. After cessation of therapy, complete recovery of the RAI uptake occurred within two weeks in most subjects. Four subjects still showed marked depression at three weeks, two at the end of six weeks and one at eleven weeks following cessation of therapy. There was no significant difference between the rate of recovery of glands depressed only a few days and that of those depressed for several years.

Progesterone. The administration of 25 mg. of progesterone daily for three days to three adult women was found by Zingg and Perry [*136*] to inhibit the radioiodine uptake by the thyroid gland. Prior to administration of the drug the thyroid uptake of I^{131} was from 1.5 to 2.2 per cent per hour, whereas following the course of progesterone the uptake was depressed to 0.6 to 1.2 per cent per hour.

Zingg and Perry [*136*] also studied the effect of *desoxycorticosterone* acetate on the thyroidal radioiodine uptake. They administered 10 mg. daily of this steroid for three days to twelve subjects. Six of the twelve persons responded with a decrease in the I^{121} uptake to below 50 per cent of initial values.

Testosterone was found to lessen the radioactive iodine thyroidal uptake by 6 to 15 per cent of the administered dose in five of six dwarfed prepuberal children receiving 25 mg. of methyltestosterone orally three to four times daily for a period of forty days [*60*].

Seven women with advanced carcinoma of the breast who received 50 mg. of testosterone propionate intramuscularly three times a week for periods from fifteen to fifty-five days were also studied. The twenty-four-hour thyroidal I^{121} uptake of four fell slightly (exact figures not given) during medication, in two patients there was no change, and in one patient there was a rise in the uptake. In twelve of the total of thirteen cases in this study the protein-bound iodine level in the serum fell significantly. In none of the patients was there evidence of hypothyroidism. The cause of these changes is not known.

Estrogens. Studies of the effects of estrogens on the I^{121} thyroidal uptake in a small group of euthyroid patients showed no consistent changes [*136*]. Animal studies, however, suggest

that the administration of estrogen would be expected to raise the twenty-four-hour thyroidal uptake. Increase of the serum precipitable iodine after administration of estrogens was documented in all sixteen patients studied by Engstrom and his group [*33*].

Soliman and Reineke [*108*] determined that the accumulation of iodine by the thyroid in the female rat is at its maximum during estrus, that estrogens in small doses consistently increase the thyroidal iodine collection, and progesterone decreases it. Feldman [*37*] studied the thyroidal I^{131} uptake after administration of estrone to castrated male rats, some of which were also adrenalectomized. The radioiodine thyroidal uptake was more than double in both treatment groups, as compared to control animals receiving saline solution. The presence or absence of the adrenal did not influence the effect.

ANTIBIOTICS

Animal experiments suggest that antibiotics may have important effects on I^{131} thyroidal uptake. Despite the common use of these agents in patients requiring thyroid function studies, this question has received little experimental study.

Grant [*43*] gave chlortetracycline (Aureomycin®) to rats and found no change in the size of the thyroid gland but there was a small increase in the thyroid I^{131} uptake. Colesnick, Harris and Jones [*29*], however, found opposite results in rats tested with iodine tracer after administration of either chlortetracycline or penicillin G. In these rats the thyroidal I^{131} uptake was decreased to 27 per cent of control values and the thyroid glands were increased in weight, suggesting a goitrogenic effect.

Chloramphenicol (Chloromycetin®) added to the diet of rats increased thyroid weight and thyroid iodine content when administered over extended periods [*118*]. No radioiodine studies were performed, however. The antithyroid effect was potentiated by additional dietary iodide and was prevented by adding desiccated thyroid to the diet.

RENAL STATES

It is important to consider the effects of renal disease on the uptake of iodine by the thyroid gland. Topics that can be conveniently grouped under this heading include increased glomerular filtration, mercurial diuresis, low serum chlorides, decreased glomerular filtration caused by renal disease and by congestive heart failure, and the nephrotic syndrome.

Increased Glomerular Filtration. Increased glomerular filtration has been stated, without documentation, to cause an increase in loss of radioactive iodine and a subsequent decrease in the thyroid uptake [*86*]. However, increased glomerular filtration could only cause a net decrease in the total body pool of stable and radioactive iodine in the same proportions, inasmuch as stable iodine and I^{131} are both filtered by the glomerulus and reabsorbed in the tubule at the same rate [*65*]. Relative iodine deficiency so produced could result only in *increased* thyroid uptake.

Diuresis. The effect of therapeutic diuresis on the thyroidal I^{131} uptake has been examined by Spies [*111*]. It was shown that the rate of iodide excretion was totally unaffected by the administration of a mercurial diuretic. He found that the administration of meralluride sodium (Mercuhydrin®) to eight euthyroid patients had no effect on the six- and twenty-four-hour thyroid I^{131} uptake. In all patients the excretion of chloride during the test period following mercurial injection rose to between 250 per cent to 350 per cent of the control values. In contrast, during the same period of time the renal clearances of radioactive iodine were essentially unchanged, remaining within the range of 88 per cent to 98 per cent of the control values. This finding is of great value to the clinician since many patients with cardiac or pulmonary disease in whom the tracer test is employed for the determination of subsequent I^{131} therapy need a mercurial diuretic for treatment of edema during the period of the test.

In contrast to these findings, a high intake of sodium chloride was found to augment the amount of radioiodine excreted in the urine in both chronic and acute experiments in mice. This was associated with a decrease in the radioiodine content of the thyroid gland [*57*].

Chlorides. Cassidy and Vanderlaan [*25*] have observed two patients with low serum chlorides who had high uptakes of RAI. Additional studies on this problem have not been carried out but it is probable that iodine deficiency due to dietary iodized salt lack is the cause of the high RAI thyroidal uptake in this instance.

Decreased Glomerular Filtration. Renal disease: Decreased renal clearance of iodine was once suspected to be a cause of increased RAI uptake by the thyroid. It is known that decreased

TABLE VII
THE EFFECTS OF THYROID STATES ON RADIOIODINE THYROIDAL UPTAKE

State	Uptake
Subacute thyroiditis	
Active phase	Depressed almost to zero [*56,123*]
Recovery phase	Elevated
Hashimoto's disease	High, normal or low [*103*]
Familial goitrous cretins	High [*64*]
Hypopituitarism	Low (becomes normal after administration of thyrotropin) [*25*]
Thyroidectomized patients	High in 50 per cent of euthyroid patients due to diminished iodine storage capacity [*23,87*]
Primary hypothyroidism	Low
Hyperthyroidism	High; occasionally may be in normal range in severe Graves' disease due to rapid turnover and early peak uptake [*90*]

glomerular filtration in renal disease decreases the renal clearance of iodide [*55*]. This delays RAI excretion and prolongs retention of serum inorganic radioiodine [*16*]. However, when RAI is retained, stable iodine also is retained. Because of the lower specific activity, the thyroid can accumulate the required daily allotment of iodine with a lower uptake of I^{131}. Thus the RAI uptake at twenty-four hours may actually be lower than normal in some cases [*65*]. Perry and Hughes [*81*] observed eleven patients with renal disease: the twenty-six-hour uptake of RAI was within normal limits except in one elderly man in whom it was quite low. They concluded that the twenty-four–twenty-six-hour *in vivo* measurement of thyroid uptake of I^{131} gives reasonably accurate information in patients with decreased glomerular filtration due to renal disease.

Congestive heart failure: It has been suggested [*25*] that congestive heart failure will produce high thyroidal uptakes because of the decreased renal clearance of iodide in this condition. As already indicated, however, it has been shown that decreased glomerular filtration does not elevate the RAI uptake.

Keating and his co-workers [*59*] studied fourteen patients with decompensated heart disease who were euthyroid. The twenty-four-hour thyroidal accumulation of I^{131} averaged 16.6 per cent (±4.3 per cent standard error of the mean). The forty-eight-hour urinary excretion rate averaged 45.7 per cent (±8.8 per cent). The excretion rate was less than the normal (range: 51 to 81 per cent in forty-eight hours). The mean thyroid accumulation rate of 1.4 per cent per hour was significantly less than that of control subjects. It can be concluded, therefore, that cardiac decompensation tends to lower the I^{131} thyroidal uptake at twenty-four hours, not elevate it. The cause of this is unknown.

Nephrosis: In the nephrotic syndrome there may be a low serum protein-bound iodine in the presence of an increased twenty-four-hour thyroidal uptake of radioactive iodine in euthyroid subjects. Recant and Riggs [*85*] carefully studied this problem in sixteen patients. In only three of the sixteen was the uptake above 45 per cent (55 per cent, 71 per cent, 75 per cent). It was concluded that these values reflected hyperactivity of the thyroid due to depletion of the gland of preformed hormone. The depletion was attributed to loss of thyroid hormone in the urine as a result of the proteinuria. In view of the low salt diets these patients usually ingest, it would seem reasonable to suspect chronic iodine deficiency as a major mechanism of the observed elevation in the RAI uptake.

GASTROINTESTINAL STATES AND TECHNICAL ERRORS OF MEASUREMENT

Inasmuch as the radioiodine used in the I^{131} thyroid uptake test usually is administered orally either as a liquid or a capsule, studies relating to the technical details of administration and to the gastrointestinal tract are relevant. It is obvious that vomiting of the test dose shortly after ingestion results in lower uptake. Occasional patients will spill part of a liquid dose during the act of swallowing. Infrequently patients will pass the I^{131} capsule through the entire gastrointestinal tract without dissolution and absorption of the iodine. Furthermore, variations in the amount of the administered dose and in the measuring technics and instrumentation must all be considered [*140*].

The Malabsorption Syndrome. Keating [*59*] found that all radioiodine values in one patient with sprue were normal. A delay of I^{131} absorption was reported in only one of six other patients with sprue [*78*].

Cirrhosis of the Liver. Mueller [*76*] reported that I^{131} uptake was 50 per cent or higher in

twenty of fifty patients who had liver disease with no evidence of thyroid disease. Shipley and Chudzik [*100*] studied thirty-six patients with cirrhosis of the liver and found twenty-four-hour uptake values in excess of 45 per cent in only five of them. Other parameters of thyroid function indicated that these patients were euthyroid. These authors pointed out that hyperavidity for iodine is characteristic in iodine deficiency and that cirrhotic patients may be prone to dietary deficiencies because of prolonged malnutrition and also because of therapeutic restriction of salt. They found that the elevated uptakes seemed to be ameliorated by hospitalization and it was concluded that a pre-existing iodine deficiency, responsible for the high uptakes of I^{131}, had been corrected by diet.

Thyroid Disorders. The effects of various thyroid states upon the I^{131} uptake test are summarized in Table VII. A detailed discussion of the mechanisms of iodine trapping and metabolism in each of these conditions is beyond the scope of this article.

SUMMARY AND CONCLUSIONS

Information concerning the substances and conditions which influence the uptake of radioactive iodine by the thyroid gland has been compiled and evaluated in respect to the known pathways of iodine metabolism.

The factors which determine the normal uptake of radioactive iodine by the thyroid gland are considered and variations due to geographical and nutritional factors are discussed. In particular the dependence of I^{131} thyroidal uptake on iodine intake has been considered. Data concerning the effects of iodine excess and deficiency have been compiled. The duration of the inhibition of thyroidal iodine following the administration of iodinated compounds for radiologic diagnosis is discussed.

Clinical evidence is presented that goitrogenic foods, thiourylene derivatives, aromatic antithyroid drugs, monovalent anions such as perchlorate and thiocyanate, and certain hormonal products may lower the thyroid uptake of iodine. Experimental evidence of other antithyroid agents or dietary states which may prove of eventual clinical importance is discussed. Few conditions other than iodine deficiency, hyperthyroidism and certain unusual thyroid conditions associated with defective hormone synthesis were found to increase iodine uptake by the thyroid. The rebound which occurs following the sudden interruptions of treatment with antithyroid drugs is of particular clinical importance in diagnosis.

The relatively slight effects of mercurial diuresis and other alterations of renal function on radioiodine uptake by the thyroid are documented. Malabsorption states and other gastrointestinal diseases rarely if ever impair the absorption of an oral dose of radioiodine.

Despite the many factors which affect the interpretation of the radioactive iodine thyroidal uptake, this measurement is established as a useful diagnostic procedure.

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Combined Staff Clinic

Systemic Lupus Erythematosus

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Richard J. Cross.*

DR. DANIEL LARSON: Systemic lupus erythematosus (S.L.E.) is a disease of unknown etiology and diverse clinical manifestations [*1,2*]. In discussing this disorder we are at once confronted with the problem of definition. Whom should we include in a study of patients with S.L.E.? This is not an easy question to answer. Should we include only those with a positive L.E. preparation? This is not very satisfactory since we know that individual patients may, at some time during the course of their disease, have negative L.E. preparations, and a few without S.L.E. may have a positive L.E. preparation. Can one rely on the pathologic manifestations of the disease? This may not be a reliable criterion since little or no histologic evidence for S.L.E. may be found after a clinical course which has been completely compatible with this disease. Perhaps the most trustworthy evidence is provided by retrospective diagnosis, that is, a patient who has followed a clinical course characteristic of an inflammatory disorder of unknown etiology involving several systems, in whom at some time a positive L.E. cell preparation develops, and at autopsy demonstrates the typical splenic, renal and other lesions.

What is the incidence of this disorder? In our clinic population, in the Vanderbilt Clinic, there are in excess of 400,000 outpatient visits per year. Over the past ten years we have had a relatively constant annual number of newly discovered cases of S.L.E., usually ranging between fifteen and twenty each year. The number of people who fall under suspicion of S.L.E. is very much larger.

In examining the records of 118 patients who, over the past twenty years, have been admitted to the Presbyterian Hospital with an acceptable diagnosis of S.L.E. (i.e., polysystem disease with a positive L.E. preparation and, in twenty-nine autopsied cases, the characteristic pathologic findings) one finds that a significant number of these persons had not been on the Medical Service at any time, but were admitted to other services throughout the Medical Center with a wide variety of presenting clinical manifestations. As can be seen in Table 1, some patients were initially admitted to the Psychiatric Institute with paranoid or hebephrenic schizophrenia, or a reactive depression; this frequently occurred after the onset of steroid therapy. A number of patients have been admitted with hematologic disease of one type or another, for example, manifestations of the presence of circulating anticoagulants or of thrombocytopenic purpura; after splenectomy for the latter disorder the full-blown clinical signs of S.L.E. did not appear for as long as nine years. Two patients in our series entered the hospital with findings suggesting acute intestinal obstruction. At operation no obstruction was found, but in one case histologic examination of an excised mesenteric lymph node raised the possibility of S.L.E. An illness resembling ulcerative colitis was the presenting picture in one of our patients. A number of patients with S.L.E. have had repeated episodes of thrombophlebitis, some apparently leading to pulmonary infarction. Another group was first seen in the peripheral vascular disease clinic complaining of Raynaud's phenomenon. A number of dermatologic disorders may herald the onset of S.L.E. In addition to the "butterfly" lesion and photosensitivity, patients may complain of angioneurotic edema for months or years before the true nature of the disease is detected. Other patients have had what was described as a drug rash, or they may have complained of alopecia for several years preceding the onset of the remainder of the

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TABLE I
EARLY CLINICAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Dermatologic
Erythema nodosum
Angioneurotic edema
Erythema multiforme
Dermatitis medicamentosa
Alopecia
Purpura
Livido reticularis
Discoid L.E.
Neurologic
Jacksonian seizures
Generalized convulsive disorder
Chorea
Guillain-Barré syndrome
Transverse myelitis
Subarachnoid hemorrhage
Myasthenia gravis
Ménière's syndrome
Psychiatric
Paranoid schizophrenia
Hebephrenic schizophrenia
Suicidal attempts
Reactive depression
Hematologic
Hemolytic anemia
Coagulation defects
Thrombocytopenic purpura
Pancytopenia
Gastrointestinal
Acute intestinal obstruction
Ulcerative colitis
Peripheral vascular disease
Thrombophlebitis
Buerger's disease
Raynaud's phenomenon

TABLE II
ABNORMAL LABORATORY TESTS IN 118 PATIENTS WITH S.L.E.

Test	No.	Per cent
Cephalin flocculation	82	69
Thymol turbidity	64	54
Rheumatoid "factor"	18	15
Coombs' test	10	8
Serologic test for syphilis (STS)	34	29
Anticomplementary STS	11	9
Positive treponema immobilization	4	3

syndrome. Finally, an impressive number were first admitted to the Neurologic Institute, with a wide variety of clinical syndromes: convulsive disorders, the Guillain-Barré syndrome, subarachnoid hemorrhage, myasthenia gravis, transverse myelitis and Ménière's syndrome.

In addition to the variety of clinical patterns, one may find a bizarre array of laboratory abnormalities in this disease. The figures shown in Table II in all probability should be revised upward. Many of the patients were not followed throughout the whole course of their disease, and it is quite likely that more frequent serum sampling would have disclosed the presence of a higher incidence of abnormal reactions. The most common abnormalities were positive reactions to cephalin flocculation and thymol turbidity tests. A few persons have shown positive serologic reactions indicating the presence of the "rheumatoid factor." Since most patients with S.L.E. have polyarthralgia or polyarthritis at one time or another, differentiation from rheumatoid arthritis sometimes is extremely difficult. Almost one-third of the group had a biologic false-positive reaction to the test for syphilis at one time or another, often for years before the onset of clinically manifest S.L.E. For example, one patient with a biologic false-positive Wassermann test was treated for syphilis at the age of nine, retreated at the age of fourteen and again at the age of nineteen, and then, at the age of twenty-nine, came in to the hospital with a fulminating course and died with classical S.L.E. There is already ample evidence that in a significant number of those with biologic false-positive tests for syphilis one or another of the connective tissue diseases eventually develops. Undoubtedly, this number will increase considerably when longer follow-up periods have been completed. Of course it is quite possible to have both syphilis and S.L.E., as in four of our cases.

A manifestation of S.L.E. of great current interest is the "L.E. cell." To the best of our knowledge, the production of the hematoxylin body requires the presence of the lupus erythematosus "factor" from the patient and a source of nucleoprotein. The latter may be of human or other animal sources. The hematoxylin body, in the presence of a phagocytosis-promoting factor, goes on to form the classic L.E. cell when it has been phagocytized by a viable leukocyte.

It has been established that the L.E. factor is associated with the gamma globulin fraction. By use of electrophoretic convection, it has been possible to obtain from the serum of a patient with S.L.E. a gamma globulin fraction containing all of the L.E. cell-promoting activity. This lupus gamma globulin was then placed in a

column of a cationic cellulose exchanger, according to the method of Sober and Petersen [3]. The material was subjected to stepwise elution, increasing the pH from 5 to 7, and increasing the phosphate buffer concentration from 0.05M to 0.15M. Following this treatment an elution pattern was obtained characterized by two major peaks. The L.E. activity could be recovered regularly on the eastern slope of the second peak [4].

This L.E.-positive column fraction was examined in a number of ways. In the ultracentrifuge, it behaved as a normal non-aggregated gamma globulin, with a sedimentation constant of 7 Svedberg units. When examined in the moving-boundary electrophoresis apparatus, it moved as a single component with the mobility of gamma globulin. When the fraction was set up in agar diffusion studies, a reaction of identity with one of the components of normal gamma globulin was observed. This may be interpreted as indicating that the fraction recovered from the column has antigenic groupings which it shares with a normal gamma globulin.

Using this technic it has been possible to eliminate 97 per cent of the gamma globulin nitrogen and retain full biologic activity of the L.E. factor. Interestingly enough, there was a drop in the nitrogen-phosphorus ratio from 44 to 14.

During the past few years a great deal of interesting experimental data have been obtained which elucidate the nature of the abnormal circulating substances found in the serum of patients with S.L.E. We are fortunate in having Dr. Halsted Holman, Assistant Professor at the Rockefeller Institute, as our next speaker. He has been actively engaged in research in this field for some time, and will tell us about some of the recent developments in this area.

Dr. Halsted Holman: I shall attempt to outline some of the recent research on the L.E. cell phenomenon and indicate one current hypothesis concerning its nature. For brevity, I shall omit much experimental detail.

As Dr. Larson mentioned, there are a number of abnormal proteins which appear in the serum of patients with systemic lupus erythematosus. Most prominent among these are proteins which give rise to the formation of L.E. cells, to a positive Coombs' test, to a prolonged clotting time, and to a false positive Wassermann reaction. Occurring with lesser frequency is a protein which causes agglutination of white cells and perhaps one which causes agglutination of platelets, although the existence of the latter is still uncertain. There is also a protein which is deposited in large amounts in the glomerular lesions of patients with lupus nephritis.

With the exception of the factor which may react with platelets, all of the proteins just mentioned have been shown either to possess the electrophoretic mobility of γ-globulins, or to react with fluorescein-labelled antiserum to normal human γ-globulin. The first four of these proteins can be readily detected by simple laboratory methods and are of considerable value in the diagnosis of the disease. The others require more refined laboratory technics or can be shown only on biopsy or postmortem examination. The unifying feature of this group of proteins is their ability to react with constituents of the cells of the body. Because these proteins appear to be γ-globulins, and because they react with cell constituents, autosensitization has been considered a possible underlying cause of this disease.

Exploration of the L.E. cell phenomenon originally led to the belief that the primary alteration induced by the circulating serum factor was a depolymerization of the desoxyribonucleic acid of the nucleus of the affected cells. However Godman [5], utilizing histochemical technics similar to those which led to the original hypothesis, has conclusively demonstrated that such depolymerization does not occur; instead there is an influx of protein into the cell nuclei which are destined to become inclusion bodies in L.E. cells. This increase in protein occurs simultaneously with the observable swelling of the nucleus.

The first contribution toward understanding the phenomenon, made by methods other than those of histochemistry, was supplied by Meischer in Switzerland. He observed that when isolated cell nuclei were passed through lupus serum the residual serum was no longer capable of inducing L.E. cell formation. Starting with Meischer's initial observation, we have examined the reaction between the L.E. cell factor and cell nuclei, using nuclei obtained from the calf thymus, rabbit leukocytes and human leukocytes [6–13]. These nuclei are all capable of adsorbing the L.E. cell-inducing factor from serum. Once the factor is adsorbed to nuclei, it is not readily removed. Elution at 56°c. in isotonic saline solution will liberate only a small amount of it. Nuclei coated with

the L.E. cell factor are readily phagocytized by normal white cells, with formation of inclusion bodies identical with those seen in the usual L.E. cells.

If the nuclei are digested with *desoxyribonuclease* prior to absorption, to an extent sufficient to remove all of the DNA, the nuclei can no longer react with the L.E. cell factor. If this digestion is incomplete, the nuclei can react partially with the L.E. cell factor and will liberate that small amount of factor which they absorb if they are heated to 56°c. Digestion with *ribonuclease* does not influence the ability of nuclei to absorb the L.E. cell factor. It would thus appear that the L.E. cell factor can react directly with the cell nucleus and that the nuclear DNA appears to be essential for the reaction.

However, the whole nucleus is not necessary for the reaction. Isolated nuclear nucleoprotein can be substituted for nuclei in the absorption of lupus serum and still completely free the serum of L.E. cell-inducing capacity. As with the whole nuclei, nucleoprotein which has absorbed L.E. cell factor will not liberate it when eluted at higher temperatures. Nucleoprotein after absorption of the L.E. cell factor is readily phagocytized by viable white cells to form inclusion bodies very similar to those seen in L.E. cells. Such phagocytosis does not occur with nucleoprotein which has been exposed to normal serum. Furthermore, one can identify γ-globulin on nucleoprotein after absorption of lupus serum. If such nucleoprotein is washed many times and then stained with an antiserum to normal human γ-globulin which has been labelled with fluorescein, this anti-γ-globulin serum adheres to the nucleoprotein and gives it a brilliant fluorescence, indicating the presence of γ-globulin. It would therefore appear that the fundamental feature of the L.E. cell phenomenon is a reaction between the L.E. cell-inducing factor in the serum and the nucleoprotein of the cell nucleus.

Such a combination between a serum γ-globulin and a constituent of the cell nucleus immediately raises the question of whether or not an immune reaction is involved. The fixation of complement between L.E. serum and constituents of the cell nucleus was therefore examined. In preparation for these experiments the nucleus was fractionated in the manner indicated in Figure 1. Cells were divided into cytoplasm and nuclei. Nuclei were then

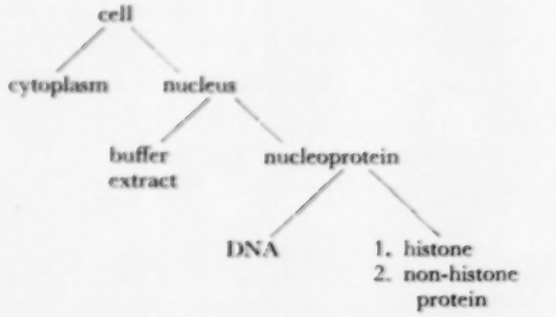

FIG. 1. Outline of fractionation of cells. For explanation, see text.

extracted with a low ionic strength buffer yielding a solution with a modest protein content. The residue from this extraction, when dissolved in one molar NaCl, gives a viscous solution which can then be spun free of residual solid materials. The viscous supernate, when brought to physiologic salt concentration, gives strands of silvery precipitate which are nucleoprotein. This nucleoprotein can be used for study and, in addition, can be further broken up into its major constituents, DNA and histone and non-histone proteins. Of these products of cell fractionation, nuclei and nucleoprotein are solid and may be readily used for absorption experiments. The buffer extract, DNA, and histone are soluble in physiologic salt concentrations, although DNA tends to form gels and therefore can be used for absorption experiments only under certain conditions.

It quickly became evident that not only did lupus serum fix complement when reacted with the whole nucleus or nucleoprotein but that it also fixed complement with other constituents of the cell nucleus. Any individual patient might react with one or more of these various constituents of the nucleus. Examples of this reactivity may be seen in Table III. Here are presented the patterns of reactivity of three representative lupus serums, all of which were capable of inducing L.E. cell formation. It will be seen that all reacted with nuclei, buffer extract of nuclei, and nucleoprotein. Two were capable of reacting with DNA but not with histone, while the other reacted only with histone and not with DNA. It may be mentioned here that the active ingredient of the buffer extract of nuclei is neither nucleic acid nor histone, for its reactivity is unaffected by either DNAse digestion or trypsin digestion.

The reactive serum factors which are responsi-

TABLE III

SERUM COMPLEMENT FIXATION WITH VARIOUS ANTIGENS

Patients	L.E. Cell Formation	Antigen Used in Complement Fixation	Serum Dilution									
			2	4	8	16	32	64	128	256	512	1024
Tr.	Strong	Nuclei	4	4	4	4	4	4	4	4	2	0
		PO_4 extract	4	4	4	4	4	4	4	4	4	0
		Nucleoprotein	4	4	4	4	4	4	4	4	2	0
		DNA	4	4	4	3	0	0	0	0	0	0
		Histone	0	0	0	0	0	0	0	0	0	0
Fr.	Strong	Nuclei	4	4	4	4	4	4	1	0	0	0
		PO_4 extract	4	4	4	4	4	4	4	4	0	0
		Nucleoprotein	4	4	4	4	4	4	4	2	0	0
		DNA	0	0	0	0	0	0	0	0	0	0
		Histone	4	4	4	4	0	0	0	0	0	0
Me.	Strong	Nuclei	4	4	4	0	0	0	0	0	0	0
		PO_4 extract	4	4	4	4	4	0	0	0	0	0
		Nucleoprotein	4	4	4	4	4	4	0	0	0	0
		DNA	4	4	4	4	2	0	0	0	0	0
		Histone	0	0	0	0	0	0	0	0	0	0

NOTE: Complement fixation between lupus erythematosus serum and constituents of the cell nucleus; serum dilution method; two 100% units of complement employed; 4 denotes complete fixation; 0 denotes complete hemolysis.

ble for the fixation of complement with nuclear antigens other than nucleoprotein and DNA have not been studied in detail. However, these factors migrate electrophoretically with γ-globulin of the serum and sediment in an ultracentrifugal field with the bulk of the γ-globulin having a sedimentation rate of approximately 7S and a molecular weight of approximately 150,000.

In view of the multiplicity of serum factors which may be present, and the variety of nuclear constituents with which they can react, it became of interest to determine which interaction between serum factor and nuclear constituent is responsible for the formation of the L.E. cell. Because isolated nuclear nucleoprotein is capable of absorbing the L.E. cell factor, it seemed likely that the nucleoprotein is the substance primarily affected during the formation of the L.E. cells. In order to test this hypothesis, it was first desirable to find a means whereby the L.E. cell-inducing factor could be recovered from the nucleoprotein.

As has been previously mentioned, after the L.E. cell-inducing factor is adherent to nucleoprotein, it is not readily liberated by exposure to higher temperatures. Disintegration of the complex by enzyme digestion was therefore attempted. Digestion by DNAse of nucleoprotein coated with L.E. cell factor liberates approximately 80 per cent of the DNA and a considerable amount of γ-globulin. The γ-globulin liberated is capable of fixing complement with whole nuclei, with nucleoprotein, and with DNA, but has a negligible capacity to induce L.E. cell formation. There remains behind after DNAse digestion an insoluble residue containing about 85 per cent of the original protein of the nucleoprotein, together with considerable amount of γ-globulin. Elution of this residue at 56°C. in isotonic saline solution frees a minimum amount of DNA and histone, but considerable additional γ-globulin is recovered. A similar recovery can be made by elution at 37°C. in 2 N NaCl. This γ-globulin fixed complement with nuclei and nucleoprotein but not with DNA. Most important, it is capable of inducing L.E. cell formation to about the same extent as the original serum. Thus it is possible to remove L.E. cell factor from nucleoprotein to which it is absorbed by first digesting the nucleoprotein with DNAse and then eluting from the residue. This stepwise procedure makes it possible to study the reaction between the L.E. cell factor and nucleoprotein, not only by the absorption of the factor from serum, but also by its recovery from the nucleoprotein. It also suggests that two bonds must be broken before the L.E. cell factor is liberated: one with DNA and another with histone (or non-histone protein) which can be ruptured only after the DNA has been split.

Exploration of the constituents of nucleoprotein necessary for binding of the L.E. cell factor was extended by removing either the DNA or the histone prior to reaction with the factor. Digestion of nucleoprotein with DNAse removes approximately 80 to 85 per cent of the DNA and leaves approximately 80 per cent of the histone and non-histone protein in an insoluble residue. Extraction of the nucleoprotein with 0.1 N HCl removes approximately 80 per cent of the histone and non-histone proteins but leaves 100 per cent of the DNA still in an insoluble form. Either procedure renders the residue incapable of reacting with L.E. cell-inducing factor, supporting the view that both of these constituents are necessary for union with the factor.

After removing the histone from nucleoprotein, it is possible to recombine the same histone quantitatively with the DNA residue. Such a recombination yields a product with only part of the capacity to react with the L.E. cell factor possessed by the original nucleoprotein. Reconstitution of nucleoprotein from which DNA has

been removed by incubating the residue with a solution of fresh calf thymus DNA gives a product with negligible ability to react with the L.E. cell factor. Furthermore, preparation of a "synthetic" nucleoprotein by reacting isolated calf thymus DNA with isolated calf thymus histone yields a substance physically resembling nucleoprotein but possessing only a fraction of the reactivity of an equivalent amount of nucleoprotein extracted from nuclei. Synthetic nucleoproteins made by substituting protamine for histone or by substituting heparin for DNA are totally incapable of absorbing the L.E. cell factor. Attempts to absorb the L.E. cell factor with isolated DNA alone have completely failed. Thus it appears that the DNA and the histone of the original nucleoprotein are essential for reaction with the L.E. cell factor, and furthermore that the configuration in which they exist on extraction from nuclei is necessary for maximum binding. In the recombination of split products or the preparation of synthetic substitutes, this precise configuration is not restored and the resulting nucleoprotein is either not as effective as extracted nucleoprotein on a milligram for milligram basis, or is totally ineffective.

The reaction between nucleoprotein and L.E. cell factor takes place at temperatures between 18°C. and approximately 45°. It may also occur at lower temperatures, but this has not been thoroughly examined. The complex of nucleoprotein and L.E. cell factor is stable at pH from 3 to 8.5. Above pH 8.5, the nucleoprotein dissolves.

The reaction between nucleoprotein and L.E. cell factor can be inhibited by prior saturation of the nucleoprotein with protamine or histone, both of which are basic proteins which are considered to block the free phosphate groups of the DNA. The reaction can also be inhibited by prior saturation of the nucleoprotein with atabrine, which is a basic material known to form stable compounds with DNA and nucleoprotein. What relation this inhibition might have to the therapeutic usefulness of atabrine in systemic lupus erythematosus is unknown. A puzzling feature of these inhibitions is that saturation of the nucleoprotein with basic methyl green, a dye which also is thought to bind the phosphate groups of DNA, does not interfere with the reaction between nucleoprotein and L.E. cell factor. Thus the nature of these inhibitions remains to be clarified.

FIG. 2. Precipitin reaction in agar between DNA and S.L.E. serum. For explanation, see text. From: DEICHER, H., HOLMAN, H. R. and KUNKEL, H. The precipitin reaction between DNA and a serum factor in systemic lupus erythematosus. *J. Exper. Med.*, 109: 97, 1959.

Recovery of active, fairly pure L.E. cell factor from nucleoprotein permitted more careful study of the characterization of this factor. The L.E. cell factor is electrophoretically and ultracentrifugally a γ-globulin. It is entirely inactivated and quantitatively precipitated by antiserum to normal human γ-globulin. When reacted in agar diffusion with antiserums to whole human serum and to isolated human 7S γ-globulin, the L.E. cell factor forms a single band of identity with these two antiserums, showing that it has the immunologic characteristics of the 7S γ-globulin. Occasionally a small amount of high molecular weight γ-globulin also may be present.

It is concluded that lupus serum may contain a variety of factors capable of reacting with different constituents of the cell nucleus. One of these reacts with nuclear nucleoprotein, is responsible for the formation of the L.E. cell, and requires both the DNA and the histone for its reaction. However, complement fixation studies showed that there was another factor capable of reacting with pure isolated DNA. The question then arose as to whether or not these factors requiring DNA for reaction were identical and, if not, whether both could induce L.E. cell formation.

The reaction between L.E. serum and DNA has been explored by Dr. Deicher in our laboratory as well as by Drs. Seligmann and Ceppellini in Europe. They have found that, in addition to the complement fixation reaction between lupus serum and DNA, there is a precipitation

reaction which can be demonstrated either in agar diffusion or by formation of classical precipitin curves. An example of the agar diffusion reaction is seen in Figure 2. Here the serum to be examined is placed at the bottom of the tube. Above it is placed a layer of agar and above that the solution of DNA. After incubation at 37°c. for a few days, a band forms in the agar. This may be seen in the tubes of the left and right which contain lupus serum. In the center is a tube containing normal serum. Treatment of the DNA solution with DNAse prior to use prevents band formation. Prior treatment with RNAse or trypsin does not interfere with development of the band.

When increasing amounts of DNA in microgram aliquots are added to a standard amount of lupus serum, a precipitate is formed in increasing amounts until a point similar to an equivalence point is reached. With further addition of DNA the amount of precipitate then diminishes in a manner similar to the diminution of precipitate in the antigen excess zone of the usual precipitin curve.

If the precipitate which is obtained at equivalence point in such a system is digested with DNAse, protein is liberated. This protein migrates as a γ-globulin electrophoretically and reacts in agar diffusion reactions against antiserum to whole human serum and to normal human γ-globulin by forming single merging band of identity. It is capable of fixing complement with nuclei and DNA, and of precipitating again upon addition of DNA. However, this γ-globulin recovered from the equivalence point precipitate is virtually incapable of inducing L.E. cell formation and the serum from which the equivalence point precipitate has been recovered still possesses most if not all of its original capacity to induce L.E. cell formation.

It thus appears that there are two factors in lupus serum which react with DNA. One, the L.E. cell factor, reacts with nucleoprotein and requires both the DNA and the histone for its interaction. The other is a factor which reacts with pure DNA and apparently is incapable of inducing L.E. cell formation. This latter statement must be qualified, however. Occasionally the γ-globulin recovered from DNA-reacting patients, when tested for L.E. cell-inducing capacity, has caused some formation of swollen nuclear material with rare appearance of L.E. cells. Whether this is the result of a primary activity of the DNA precipitator itself, of a minor cross reactivity between two factors directed against substances possessing a common reactive site, or of coprecipitation of a small amount of separate L.E. cell factor with the DNA γ-globulin complex remains to be determined.

Are these serum factors, which react with nuclear constituents, antibodies, in particular autoantibodies? All studies conducted to date have shown these substances to possess the characteristics of typical human antibody γ-globulin. The nature of their interaction with nuclear substances is consistent with a reaction between antigen and antibody. They are capable of reacting with the nuclear material of the patient from which they are recovered. However, identical factors have not yet been obtained in animals immunized with nuclear materials. Therefore, while no evidence has appeared to contradict the hypothesis that they are antibodies, the supporting evidence must be considered incomplete. The search for analogous factors in animals may prove difficult, however. If these factors arise in man because of an abnormal immune response to a normal cell constituent, their recovery from animals with normal immune responses would not be expected. This contention is strengthened by the fact that nucleic acids and histones are notoriously poor antigens experimentally and the appearance of antibodies to them in S.L.E. most likely reflects a basic abnormality in the immune responses of the patient.

The significance of the appearance of these factors remains to be determined. However, two points merit attention now. The first concerns the specificity of these complement fixation reactions for S.L.E. and the relationship of the titers of the antinuclear factors to disease activity. With regard to specificity, we have not yet found a serum from a patient with a disease other than systemic lupus which is capable of reacting with the nucleic acid constituents of the cell nucleus. However, a few cases with scleroderma, as well as some with various types of liver disease and hypergammaglobulinemia, have possessed high titers of reactivity with whole tissue extracts and at times with whole nuclei or phosphate extract of cell nuclei. Thus complement fixation reactions with cell constituents other than the nucleic acid materials of the nucleus cannot be considered a phenomenon specific for systemic lupus ery-

thematosus, at least as it is now recognized clinically.

With regard to titers, thus far we have found them to be highest during active phases of the disease and to diminish or completely disappear when the patients experience either spontaneous or therapeutic remission. The complement fixation reactions can be used as a diagnostic test, but in our experience they have not been positive in any significant number of patients with clinical systemic lupus who did not also show positive lupus cell preparations. Conversely, in a few cases weakly positive L.E. cell formation was present without evidence of complement fixation reaction. Consequently, complement fixation with nuclear antigens does not at the moment qualify as a more sensitive screening test for the presence of systemic lupus erythematosus.

Perhaps the best prospect for a simple clinical screening method for S.L.E. is that developed by Drs. Christian, Mendez-Bryan and Larson [*14*]. This consists of coating latex particles with nucleoprotein and then obtaining agglutination of these coated particles when they are mixed with lupus serum. This reaction would have the advantage of the fact that the phosphate-extractable material from the nucleus is not carried with the nucleoprotein, and therefore this test might be expected to show a high degree of specificity for S.L.E.

The second major question concerns the relationship of these circulating antinuclear serum factors to pathogenesis of the disease. At this moment, the evidence is against a causal relationship of these factors to the disease or any of its pathologic lesions, primarily because the antinuclear factors do not appear capable of crossing the cell membrane and cytoplasm of a viable cell. This evidence is: (1) L.E. cells are not found *in vivo* except under very unusual conditions; (2) children born of mothers with circulating L.E. cell factors have been found to have this factor in their blood via placental transfer, but have not suffered identifiable damage; (3) with rare exceptions, staining of postmortem lupus tissues with fluorescein-labelled antiserum to human γ-globulin has not revealed the presence of γ-globulin in the cell nuclei; and (4) we have been unable to interfere with tissue culture growth of either normal or Hela cells by addition of large amounts of high titer lupus serum to the culture medium.

There is one biologic activity, however, of which at least one antinuclear factor is capable. Lupus serum, in direct relation to the presence of DNA precipitating factor, will inhibit bacterial transformation in pneumonococci. This effect, however, requires isolation of DNA from one type of bacteria, exposure of the DNA to the lupus serum, and then passage of the DNA to the other type of bacteria. Thus the factor is not required to enter a viable cell before combination with DNA, and this biologic activity is not in contradiction to the general failure of these circulating factors to gain access to the nuclei of viable cells.

Nevertheless, these conclusions concerning the possible biologic and pathologic role of the antinuclear factors must be considered entirely provisional. It is possible that more thoughtful experimental design in the future will yield evidence for far more complicated and significant actions of these factors.

In summary, patients with systemic lupus erythematosus, already known for their propensity to form what are apparently antibodies to many different body tissues, now appear able to form a family of antinuclear factors resembling antibodies. The latter are of particular interest because of the known poor antigenicity of nucleic acids; S.L.E. may yield the first good evidence of their antigenicity. The appearance of such factors which react with the patient's own cell materials strengthens the contention that autoimmune mechanisms are at work in this disease. Whatever the future may bring by way of clarification of the nature and biologic role of these factors, study of their reactivities and of the presumably unusual immune response which gives rise to them should increase our understanding of autoimmunity in general and the causes of this disease in particular.

Dr. Larson: Polystyrene ("latex") particles of approximately 0.8 microns in diameter carry an electrical charge on their surface. Under appropriate circumstances [*4*] these particles may become coated with nucleoprotein. When a suspension of coated latex is placed in the serum of a patient with circulating L.E. factor, agglutination of the particles usually results [*14*]. Dr. Charles Christian has carried out a number of absorption studies using this L.E. agglutination technic. Unabsorbed serum from patients with S.L.E. may agglutinate coated latex particles in dilutions up to 1:32 or higher. S.L.E. serums which have been absorbed with coated latex fail to give further agglutination. Of even

TABLE IV
L.E. AGGLUTINATION TEST

Disease	No.	Positive L.E. Preparation	Positive Agglutination
Miscellaneous	131	..	0
Connective tissue disease	57	..	0
S.L.E.	33	20	26
Agglutination failures	3	3	0
Non-specific agglutination	7	0	7

greater significance is the observation that the L.E. cell-promoting factor itself can be completely absorbed out of L.E. serums by the use of coated latex.

Studies on the L.E. agglutination reaction indicate that DNA, in relatively low concentrations, is capable of inhibiting the reaction. When the DNA is previously treated with desoxyribonuclease, however, the DNA loses its ability to inhibit the agglutination. RNA, desoxyribose and histone fail to inhibit the reaction.

We have examined the serums from 221 patients, using this technic. Not one of 131 patients with a wide variety of disorders (other than S.L.E.) gave a positive reaction to agglutination test. (Table IV.) Fifty-seven patients with so-called diseases of the connective tissue, most of whom were clinically diagnosed as having rheumatoid arthritis, also had a negative result. Serums from thirty-three patients with well documented S.L.E. have been tested, and twenty-six of them gave a positive reaction. Six of these had a positive agglutination test at the time their L.E. preparations were negative. In three patients with clinical S.L.E. and a positive L.E. preparation the coated particles failed to agglutinate.

Of considerable importance is the observation that serums obtained from seven persons agglutinated not only coated particles but uncoated particles as well; all seven of these patients, so far as we know, do not have S.L.E. For this reason it is necessary to include in the test an uncoated latex particle control. This type of reaction has been previously described in connection with a search for "rheumatoid factor" using the FII latex technic [*15*].

One of the most distressing features of S.L.E. is the high mortality rate due to renal involvement. Dr. Arthur Snyder has recently reviewed the coincidence of the nephrotic syndrome and S.L.E. in our clinic and has some interesting data to present at this time.

DR. ARTHUR SNYDER: That clinical indications of renal parenchymal disease are one of the protean manifestations of systemic lupus erythematosus has been recognized for many years. The incidence of renal involvement, when persistent proteinuria in the absence of fever, dehydration and urologic abnormalities is taken as the clinical criterion, is high, ranging from 50 to 75 per cent in various reports in the literature. The true incidence of renal involvement in S.L.E. is even higher, however, since biopsy and autopsy studies reveal that pathologic changes in the kidney are present in patients in whom there are no abnormalities of the urinary sediment or signs of renal insufficiency.

The clinical course of renal involvement in S.L.E. is extremely variable. Of a group of patients with systemic lupus studied here, many had persistent proteinuria without clinical or laboratory evidence of renal insufficiency, which remained unchanged for many years. In others, rapidly progressive renal insufficiency developed.

It is difficult to establish with certainty how frequently renal insufficiency is the cause of death in patients with S.L.E. In a recent Johns Hopkins Hospital study [*2*], thirty-eight patients were examined at autopsy. Twenty-two patients of this group were considered to have died as the result of progression of S.L.E. In nine of these renal insufficiency was considered to be the immediate cause of death, although other factors played a role in several of these patients.

The studies of Muehrcke et al. at the University of Illinois have done much to clarify the histopathology of the developing kidney lesion [*16*]. These workers made a systematic analysis of single and serial percutaneous renal biopsy and autopsy specimens, paying careful attention to the problem of sampling. Employing the light microscope, they found that the earliest detectable lesions of lupus nephritis were confined to the glomeruli. In what appeared to them to be basement membrane, small areas of irregular local thickening were found at the periphery of the glomerular tufts. In almost all instances this change was associated with local proliferation of endothelial cells. In many cases this local and focal glomerulitis gradually progressed, and features more peculiar to lupus nephritis then appeared. Among these were local fibrinoid changes, hematoxylin bodies,

and occasionally hyaline thrombi in the glomerulus. When thickening of the glomerular basement membrane and fibrinoid changes became predominant features, the so-called wire-loop lesions were seen. In areas of local necrosis, the glomerulus frequently became adherent to Bowman's capsule. These local adhesions then underwent organization and fibrosis; when these lesions were more extensive, proliferation of epithelial cells was observed, and crescent formation was seen. The typical histologic picture of chronic glomerulonephritis, however, fibrosis and hyalinization of many glomeruli, was distinctly uncommon. Tubular, vascular and interstitial changes were not seen in the early stages, but as glomerular lesions became more pronounced, tubular degenerative changes, interstitial infiltrates and edema were found. Vascular changes occurred only late in the disease.

Dr. Marilyn Farquhar of the Rockefeller Institute has made interesting electron microscopy studies of the glomerulus in S.L.E., as have Kark and others. Some of the changes are seen by this technic before they are visible with light microscopy. Magnification of the normal glomerulus section under the electron microscope reveals three chief glomerular components: endothelium, basement membrane and epithelium. Thickening of the basement membrane has been found to be the most characteristic lesion of S.L.E. This change is found irregularly throughout the glomerulus but tends to occur in the capillaries at the periphery of the tuft. Fibrinoid material is deposited between the endothelial cell and the basement membrane. The morphology of the epithelial cell in the early stage is entirely within normal limits. A few patients studied by Dr. Farquhar after steroid treatment was begun demonstrated a decrease in fibrinoid without detectable changes in the basement membrane.

The nephrotic syndrome observed during the course of the renal involvement in S.L.E. is considered currently to be the metabolic, nutritional and clinical consequence of massive proteinuria. In addition to proteinuria, hypoalbuminemia and edema are considered cardinal signs. Increased glomerular filtration of plasma protein is the predominant cause of the proteinuria, but impaired tubular absorption of protein may also play a role in some patients.

In the past two decades 322 patients with nephrotic syndrome of all etiologies were seen at the Presbyterian Hospital. Of these, 126 were females, 211 had the onset of nephrotic syndrome before the age of ten. In the past two decades, 189 patients who met our clinical criteria for definite or probable S.L.E. were seen here. The presence of the L.E. cell phenomenon was regarded as confirmatory evidence for the diagnosis. (Table v.)

TABLE V

COINCIDENCE OF THE NEPHROTIC SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical Description	No. of Patients
Total number with nephrotic syndrome	322
Under ten years of age	211
S.L.E.	1
Between ten and fifty years of age	81
Female	48
Female with S.L.E.	17
Male	33
Male with S.L.E.	2
Over fifty years of age	30

Twenty patients were found to have both diagnoses—S.L.E. and nephrotic syndrome. Other causes of the nephrotic syndrome could not be established in these patients. In addition to the nephrotic syndrome, other features of S.L.E. were regularly found in these patients. Eighteen of the twenty patients studied were female, and they did not differ from other patients with S.L.E. with respect to their age at the onset of their disease. Nineteen of the patients were between ten and fifty years of age at the onset of the nephrotic syndrome. Seventeen of these patients were female.

Of the 322 patients with nephrotic syndrome of all etiologies, the onset of the disease was noted between the ages of ten and fifty in eighty one. Forty-eight of these were female. Thus of a total of forty-eight female patients with the onset of nephrotic syndrome between the ages of ten and fifty, seventeen were found to have S.L.E. In comparison, the incidence of S.L.E. in the male adult population with the nephrotic syndrome was only two of thirty-three patients. Between the ages of ten and fifty, there were more women with the nephrotic syndrome than men, and this difference in incidence appears to be due to the large numbers of female patients with S.L.E.

In our study of twenty patients with both

S.L.E. and the nephrotic syndrome, the development of edema was taken as indicating the time of onset of the nephrotic syndrome and for admission of the patient to the study group. In all patients, edema was associated with hypoalbuminemia and persistent proteinuria. Serum cholesterol concentrations were elevated at some time during the course of sixteen of our twenty patients; observations were incomplete in the remaining four. Microscopic pyuria and hematuria were noted in all of the patients.

When the patients were first examined, the blood urea nitrogen concentrations ranged from 9 to 135 mg. per cent. Nine of the twenty patients had blood urea nitrogen values greater than 25. At the time of the initial examination definite hypertensive blood pressure levels were present in only four of the group. Despite remission of the nephrotic syndrome, which by our criteria was disappearance of the edema and elevation of the serum albumin to normal, all the patients showed persistent proteinuria.

A wide variation was noted in the time interval between the onset of S.L.E. and the appearance of the nephrotic syndrome. In one patient the nephrotic syndrome was a presenting feature of S.L.E. The other extreme is represented by the patient in whom the nephrotic syndrome appeared thirteen years after the first clinical evidence of S.L.E. In two-thirds of the patients the nephrotic syndrome developed one year or more after the onset of the disease; in half, a three-year interval intervened.

The appearance of the nephrotic syndrome did not necessarily herald a phase of progressive renal failure, although this was the most common cause of death in the entire group of patients. Ten patients survived the nephrotic syndrome more than one year and two patients were still alive at least three and a half years later. However, ten patients died within the first year after the appearance of the nephrotic syndrome. These two groups were examined to determine if any feature of the clinical picture characterized either of the groups. Of the ten patients who survived the onset of the nephrotic syndrome less than one year, in five the appearance of S.L.E. had been noted within the preceding seven months. Of the ten patients who survived the onset of the nephrotic syndrome more than one year, in only two had the appearance of S.L.E. been noted within the preceding seven months; in the remaining eight patients an interval of at least eighteen months was noted between onset of systemic disease and the nephrotic syndrome. These observations suggest that, considered as a group, the prognosis is poorer the earlier the onset of the nephrotic syndrome in the course of S.L.E. In considering individual patients, there were notable exceptions to this observation. The appearance of the nephrotic syndrome was not, *per se*, a poor prognostic sign. Considered as a group, the early appearance of the nephrotic syndrome in S.L.E. reflected the tempo of progression of the underlying systemic disease and thus reflected prognosis in a general way. The two groups were not unlike when compared with regard to the frequency of the presence of azotemia, hypertension, the severity of the nephrotic syndrome as measured by hypoalbuminemia, or duration of the nephrotic syndrome as measured by the interval between the onset and disappearance of edema. These parameters of renal involvement appeared to bear no relation to the prognosis.

In a consideration of the treatment of the nephrotic syndrome, it should be noted that the majority of our patients were given only modest dosages of steroids. Sixteen of our twenty patients received steroid treatment at some time during the course of their nephrotic syndrome. Ten patients received doses of prednisone greater than 30 mg. daily for at least one week, and four received this dose for at least three weeks. Two patients received 100 mg. of prednisone daily for ten and twenty-one days each.

There appeared to be no clinical response to treatment except in two patients. However, these two patients were receiving diuretics at the same time, and further consideration of their courses makes it seem unlikely that the observed diuresis could be attributed to the effect of the steroid. Our experience thus has been similar to that of others: given in this dosage for this duration, steroids had no detectable influence on the course of the nephrotic syndrome in S.L.E.

To date, no clinic has produced convincing evidence that steroid treatment in any way alters the natural course of lupus nephritis. Observers from several clinics have been intrigued by the possibility that very large doses of steroid, administered early, may reverse the pathologic processes. Failure to produce any change in the thickened glomerular basement membrane, the most consistent abnormal finding in the glomerulus, does not support this hope,

but further experience will be necessary for definitive judgment.

In a consideration of the treatment of S.L.E. in general, it is apparent that the administration of steroid has an immediate and salutary effect on the patient with acute systemic disease. There is no clear evidence that a decrease in the incidence of untoward effects, such as the development of peptic ulcer or osteoporosis, and the aggravation of diabetes, has been accomplished with the newer steroids which potentiate their anti-inflammatory effects without a concomitant increase in their action on electrolytes.

Since there is neither clinical nor pathologic evidence that the fundamental abnormalities in this disease are altered by steroids, and since steroid treatment, even with the newer drugs, is fraught with the danger of untoward reactions, the policy of our clinic has been to restrict the use of steroids until such time as the severity of the clinical problem warrants their use. Until such time, our patients receive palliative treatment with less potent and less toxic anti-inflammatory agents, such as aspirin and chloroquin.

Dr. Larson: This completes the formal presentations. We would welcome any comments or questions from the audience.

Dr. Elvin Kabat: Because a material reacts with DNA or with DNA-protein, the DNA is not necessarily the "antigen" which provided the initial stimulus to formation of the material. Many years ago it was found that horse antipneumococcus serum would precipitate specifically with DNA. If we didn't happen to know that the horse had been immunized with a pneumococcus containing the specific capsular polysaccharide antigen, and if we had just taken this serum as one occurring in the course of a natural disease of horses, we might have said that the DNA was the antigen.

Further efforts, in terms of our basic immunochemical knowledge, to break down the relationship of DNA, DNA-protein and the circulating abnormal proteins in S.L.E. are of the utmost importance. In this connection I would like to ask Dr. Holman, what is the pH range at which the precipitin reaction with DNA and these factors occurs?

Dr. Holman: We concur with Dr. Kabat's caution regarding overinterpretation. However, I do not believe that the horse antipneumococcal serum reaction with DNA is comparable to that of L.E. serum. DNA is known to precipitate non-specifically with many proteins, including γ-globulins at pH's below 7. Presumably this is due to electrostatic interaction because at these low pH's the net electric charge of the DNA is negative while that of many of the reactive proteins, at these low pH's below their isoelectric points, is positive. Such precipitations usually do not yield a precipitin-like curve; rather, the amount of precipitate continues to rise as nucleic acid is added and no "antigen excess" phenomenon is observed. Dr. Deicher has observed this type of reaction, at these pH's, between DNA and normal human serum or normal human γ-globulin.

The horse antipneumococcal precipitation with nucleic acids is presumably this type of non-specific interaction because it occurs only at pH's below 7. Furthermore, these hyperimmunized horse serums usually contain large amounts of easily precipitable euglobulin which leaves solution readily on minimal dilution.

The precipitin reactions with L.E. serum have been carried out between pH 7 and 8.6. In this range both γ-globulin and DNA are negatively charged and electrostatic interaction would be unlikely. Precipitin type curves are obtained. In this pH range, no other serum tested yielded any precipitate whatsoever. Finally, the L.E. serum which gave the precipitin reaction had only normal amounts of euglobulin.

Dr. Kabat: May I just ask one other question? What is the isoelectric point of the L.E. factor that you have isolated?

Dr. Holman: We have not determined it specifically but it migrates as a gamma globulin and we presume it has approximately the same isoelectric point as gamma globulin.

Whether or not the L.E. cell factor migrates with the more basic or the more acidic γ-globulin is an unresolved question. Some workers believe it travels in the basic region, and therefore it might have a slightly higher isoelectric point than the mean value for γ-globulin. However, we have always found it on the acid side of the γ-globulin peak after starch electrophoresis. Perhaps the issue can be settled now that methods are available for obtaining reasonably pure factor.

Dr. Larson: There has been considerable interest in the use of high dosages of steroid in the therapy of the renal lesion of S.L.E. I wonder, Dr. Holman, if you are in complete agreement with Dr. Snyder's point of view?

Dr. Holman: We are impressed with the usefulness of steroids in the treatment of both

lupus nephritis and lupus nephrosis. However, we have not conducted studies specifically designed to evaluate therapy and therefore our thoughts must be considered provisional.

In the past three years we have treated some forty patients with S.L.E. A majority of these have shown some degree of kidney disease, varying from minimal proteinuria and hematuria to advanced disease of the kidney with anasarca, azotemia, hypertension and massive hematuria. Our treatment has been virtually the same in all cases. The patients begin with a regimen of approximately 60 mg. of meticorten administered daily, plus antimalarials. The steroids are reduced to levels of 30 to 50 mg. of meticorten administered daily as soon as clinical improvement appears. These dose levels are maintained until the sedimentation rate, hemoglobin, γ-globulin and albumin return to or toward normal, and the disease of the kidney has either disappeared or stabilized. When this point is reached steroids are gradually discontinued and the patients are maintained on antimalarials.

Most cases with minimal or moderate renal disease have had a return to normal of their kidney status, as judged by the absence of hematuria, normal twenty-four-hour urinary protein, and normal urea clearance. All but one of the patients with advanced renal disease have had such striking improvement that they are now carrying on normal or near normal activity, and are receiving either no therapy or only small doses of medication. One patient experienced a loss of 70 pounds of edema fluid, a drop in blood urea nitrogen from 100 mg. per cent to normal, and complete disappearance of marked hematuria. Hypertension remains, however. Two young women with typical nephrosis now have entirely normal kidney function, although neither is receiving steroids at this time.

The difference between the results reported by Dr. Snyder and those we seem to be having may in part be accounted for by the difference in the dosage of steroids used and the length of treatment. He indicated that the maximum duration of treatment in this series was about thirty days and that doses of meticorten above 30 mg. daily were used only briefly. We have rarely seen significant improvement in that period of time with that dose of steroids in any patient having more than minimal renal involvement. The duration of treatment in our patients has varied from two months minimum to eight months maximum before steroid withdrawal. In the more advanced cases the average steroid dose has been about 50 mg. daily, but in all these instances the steroid dosage has now been reduced or discontinued, without significant relapse to date.

Whatever the final decision may be with regard to the over-all efficacy of steroids in lupus renal disease, the fact that some people do appear to benefit might indicate that longer term therapy should be attempted than is now commonly used.

SUMMARY

Dr. Richard J. Cross: Systemic lupus erythematosus is a chronic, progressive disease of undetermined etiology. Studies of its incidence have been hampered by the lack of clear-cut criteria for diagnosis, but in recent years it has become apparent that this disease is far more common than was once thought and that it has frequently been confused with a wide variety of other conditions. Its clinical and laboratory manifestations are highly variable, and certain of them may occur many years before any other evidences of the disease are observed.

It is usually possible, at some stage of the disease, to find in the serum of patients with systemic lupus erythematosus one or more of a group of abnormal γ-globulins. The most constant of these is the L.E. factor, which promotes the phagocytosis of nucleoprotein. Complement is fixed when this factor reacts with nucleoprotein, a reaction which appears to involve two bonds, one with DNA and one with histone. Other factors in the serum also are capable of reacting with nucleoprotein or with other fractions prepared from nuclei. These factors appear to be antibodies, and their presence suggests that autoimmune mechanisms play a role in the development of this disease. But these factors do not seem to be able to cross the cell membrane of living cells, and thus there is doubt that they directly contribute to the pathogenesis of systemic lupus erythematosus.

A useful diagnostic test for S.L.E. has been developed, based on the agglutination of latex particles which have been coated with nucleoprotein.

Renal involvement is commonly encountered in this disease and is a frequent cause of death. Some investigators have reported good results from prolonged administration of steroids in high dosage; others have been less successful.

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Clinicopathologic Conference

Staphylococcal Sepsis and Acute Renal Failure

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, a fifty-two year old Negro part-time minister, part-time cotton picker was transferred to the Barnes Hospital on June 14, 1959 because of renal failure. He died on June 18, 1959.

In 1940 he had severe pain in the lower part of his back after chopping wood. Thereafter, he was never able to perform heavy lifting. Exacerbations of this pain caused his separation from the Army in 1943 and caused him to seek medical attention in 1959, after chiropractic manipulations had failed to relieve him. He entered the University of Missouri Hospital in February 1959 and on physical examination was found to have evidence of right lumbar nerve root compression. A myelogram was interpreted as showing herniated nucleus pulposus in the L5-S1 interspace. Other studies were within normal limits. Laminectomy was advised, but the patient declined.

On March 5, 1959, he entered the St. Louis Veterans Administration Hospital, because of pain in the lower part of his back. Additional history revealed good general health. He had had a heavy alcoholic intake until several years before admission; at age eighteen he had an illness diagnosed as gonorrhea, which was treated with two injections of "606." The physical examination was within normal limits except for the presence of poor oral hygiene, a right lumbar scoliosis, and paravertebral muscle spasm in the lumbar area. The right knee and ankle jerks were considered to be hypoactive and a questionable area of hypalgesia was present on the right leg.

On admission, the chest roentgenogram, blood counts, serum electrolytes, blood urea nitrogen, sugar, calcium, and alkaline phosphatase were within normal limits. The urine had a specific gravity of 1.026, contained no protein or sugar, and had an occasional white blood cell and red blood cell on microscopic examination.

On April 16 laminectomy was performed and a herniated nucleus pulposus at the L4-5 interspace was removed. On the first postoperative day the temperature rose to 38.4°C.; this was attributed to atelectasis. The fever persisted with temperatures in the range of 40°C., and additional studies were undertaken. On the third postoperative day, a roentgenogram of the chest was interpreted as showing atelectatic areas at the right base. The hematocrit was 33 per cent; the white blood cell count 14,000 per cu. mm. with a shift to the left; the urine contained 2-plus protein, and many hyaline and coarsely granular casts; the electrolytes were normal. A culture of the urine grew Beta hemolytic streptococcus; the sputum on culture contained both coliform and mucoid lactose fermenting organisms. A battery of agglutinations was negative.

Therapy with procaine penicillin (600,000 units administered every eight hours) and streptomycin (0.5 gm. administered every eight hours) was begun on April 19; and when the temperature rose to 41°C. on April 20 the penicillin dosage was increased to 500,000 units of crystalline penicillin given every four hours.

Because of continued fever, a needle was inserted into the area of the wound on April 21. A small amount of serous material was aspirated which contained large numbers of coagulase positive hemolytic Staphylococcus aureus on culture. On April 22, incision into the laminectomy area was performed and 15 ml. of seropurulent material was drained. A fall in systolic

blood pressure to 88 mm. Hg occurred postoperatively and unit of blood was given. A lumbar puncture revealed uninfected spinal fluid. Heavy growth of Staph. aureus was obtained in a blood culture at this time. The organism from the back wound was sensitive to chloramphenicol, penicillin, streptomycin, novobiocin, bacitracin, tetracyline, erythromycin and polymyxin. The organism from the blood was sensitive to each of these antibiotics except penicillin, to which it was only slightly sensitive. Sensitivities were performed by disc method.

On April 22, penicillin and streptomycin therapy was discontinued, and treatment with chloramphenicol and erythromycin was begun; each was given in the dose of 2 gm. per day. Erythromycin was given for one week, and chloramphenicol for two weeks. The temperature gradually fell from 40° to 37°C. by April 30 and the patient felt better; a blood culture drawn on May 6 was sterile. He remained afebrile until May 16. During this period extensive investigation of the gastrointestinal tract was undertaken because of abdominal distention and cramping; no lesions were noted.

On May 16 the temperature rose to 38.6°C. and within two days daily spikes to 40.5°C. were occurring. The patient was experiencing moderately severe pain in the hip and back, and had lost considerable weight. Studies at that time showed a trace of protein in the urine, a hematocrit of 31 per cent and a white blood cell count of 18,000 per cu. mm. Fluoroscopy of the chest revealed motion of both diaphragms; roentgenograms of the spine and hip were within normal limits except for the laminectomy defect. Chloramphenicol therapy was reinstituted and the patient was given 2 units of blood; a blood culture on May 27 again was positive for Staph. aureus. The wound contained pseudomonas in large numbers. Disc sensitivities on the staphylococcus from the blood stream revealed it to be sensitive to erythromycin, novobiocin, bacitracin, kanamycin and vancomycin, but resistant to chloramphenicol, streptomycin, penicillin and tetracycline.

On June 2 therapy with novobiocin, 500 mg. administered every six hours, was instituted, and chloramphenicol therapy was discontinued, but the temperature spiked to 39.5°C. each day until his transfer, and he continued to have back pain. On June 9 through June 12 the back wound was radiated. A total dose of 1,200 r in air was administered. On June 12, the patient complained of anorexia. Because of weight loss, Nilevar® therapy was begun. Since it was noted that the patient had not voided, an indwelling catheter was placed in the bladder, and 150 ml. of dark, turbid urine with specific gravity of 1.015 was obtained. He was given 1,000 ml. of 5 per cent glucose in water and 1,000 ml. of Ringer's lactate solution intravenously and 1,000 cc. of water orally, but he passed only 100 ml. of urine in the succeeding fifteen hours. On June 13, after the ingestion of 1,400 ml. of oral fluid, the fluid intake was restricted to 500 ml. 50 per cent glucose in water with insulin added; the urinary output was between 1 and 3 ml. per hour and the urine contained 1-plus protein, a few granular casts, a few white blood cells and many bacteria. The white blood cell count was 19,000 per cu. mm., the hematocrit 26 per cent, the blood urea nitrogen 80 mg. per cent, sodium 129 mEq. per L., potassium 7.2 mEq. per L., carbon dioxide 17 mEq. per L. and chlorides 84 mEq. per L.

On June 14 slow infusion of 50 per cent glucose solution was continued, the urinary output was 1.5 ml. per hour until 4:00 A.M., after this time no flow was observed. Several tap water enemas were given. The blood urea nitrogen was 142 mg. per cent, sodium 126 mEq. per L., potassium 5.4 mEq. per L., carbon dioxide 16.1 mEq. per L., chloride 84 mEq. per L. A chest roentgenogram was read as "infiltrate in the inferior portion of the left lung and an infiltrate with a central radiolucent area in the left upper lung field." The colon was dilated and the kidneys were of normal size on a flat film of the abdomen. An electrocardiogram was not suggestive of hyperkalemia. The patient was transferred to Barnes Hospital in the midafternoon of June 14.

On physical examination the temperature was 38°C., respirations 24 per minute, pulse 110 per minute and blood pressure 120/70 mm. Hg. The patient was a husky muscular Negro man who was lethargic and breathing deeply. The skin was dry and scaly with fairly good turgor; a clean granulating surgical wound was present over the midline in the lumbar area. The epitrochlear lymph nodes were enlarged, a small soft node, 5 mm. in diameter, was present in each axilla. Shotty lymph nodes were palpable in the inguinal areas. The scleras were icteric, the pupils reacted well, and the fundi were normal. The mucus membranes of nose and throat were dry. The chest was symmetrical and respirations

TABLE 1

PERTINENT LABORATORY DATA

Date	Fluid Intake (ml./day)	Urine Output (ml./day)	Weight (lb.)	Blood Levels						
				Sodium (mEq./L.)	Potassium (mEq./L.)	Carbon Dioxide (mEq./L.)	Chloride (mEq./L.)	Calcium (mg. %)	Phosphorus (mg. %)	Urea Nitrogen (mg. %)
6/12	3,000	210	.....	...	...	....	..	...	...	...
6/13	1,900	68	.....	129	7.2	17	84	...	...	80
6/14	500	6	166.5	126	5.4	16	84	7.4	5.2	142
6/15	600	15	165.5	117	4.7	19.5	87	...	...	127
6/16	1,500	10	162.25	123	4.7	18.6	83	...	...	133
Dialysis										
6/17	700	30	166.0	130	4.9	18.3	92	7.5	7.2	166
6/18	300	50	165.0	...	...	....	..	...	...	...

were deep and rapid. Moist rales were heard at the left posterior base; these disappeared after coughing. The left border of cardiac dullness was 9½ cm. to the left of the midsternal line in the fifth interspace. No gallop rhythm was heard. A soft systolic grade 2 murmur was heard at the left sternal border, A_2 was equal to P_2; the liver was firm and non-tender; it extended 4 cm. below the right costal margin. There was moderate abdominal distention; bowel sounds were hypoactive. No splinter hemorrhages were present. Straight leg raising was limited bilaterally; there was a coarse shaking tremor, and generalized hyperreflexia. No sensory deficit was present.

The laboratory data were as follows: Hemoglobin 8.6 gm. per cent, white blood cell count 17,550 per cu. mm., differential: 10 per cent stabs, 75 per cent segmented forms, 12 per cent lymphocytes and 3 per cent monocytes. The red blood cells were hypochromic. Platelets were thought to be decreased on smear. The urine contained 2-plus protein, and no sugar. On microscopic examination of the urine there were occasional white blood cell casts and granular casts; 5 to 10 white blood cells were present. Reaction to the serological test for syphilis was negative; the stool was guaiac negative. See Table 1 for additional laboratory data. The total protein was 6.3 gm. per cent with albumin 2.4 gm. per cent, globulin 3.9 gm. per cent, cephalin cholesterol flocculation 4 plus, thymol turbidity 9.6; Van den Bergh (before chloroform extraction) 5.9 mg. per cent, 3.1 direct, 2.8 indirect; Van den Bergh (after chloroform extraction) 4.8 mg. per cent, 2.4 indirect; serum glutamic oxalacetic transaminase 52 units, serum glutamic pyruvic transaminase 2 units. The prothrombin time was 70 per cent of normal; clotting time six minutes. Electrocardiograms taken on admission and on the third hospital day were interpreted as showing an abnormal form of ventricular complex; an electrocardiogram taken on the fourth hospital day was interpreted as showing anterior myocardial ischemia. Culture of blood drawn on admission had profuse growth of Staph. aureus, which grew in all concentrations of erythromycin and penicillin, was inhibited by 20 μg. per ml. of novobiocin, and did not grow in 1 μg. per ml. of vancomycin. Urine culture was sterile. The venous pressure was 70 mm. of saline and the circulation time 14 seconds. A roentgenogram of the chest was officially interpreted as being within normal limits except for tortuous aorta, however, unofficially it was thought to show an elevated left diaphragm and areas of infiltration suggestive of abscesses. Abdominal roentgenograms were compatible with ileus, although no gas was seen beyond the distal sigmoid. There was no evidence of obstruction on barium enema. A blood culture on the fourth hospital day was sterile.

On admission the patient was placed on respiratory and contact isolation; the administration of 50 per cent glucose in water was continued at a slow rate; novobiocin therapy, 1 gm. given every six hours, was continued. Basaljel® was administered orally. Because of the anuria, retrograde ureteral catheterization was performed on the left to rule out obstruction. The injection of radiopaque dye showed a normal left renal pelvis and ureter. The left kidney was considered to be of normal size. Four ml. of turbid urine was collected from the bladder; this was sterile on culture. Because of the ques-

tion of subdiaphragmatic or intra-abdominal abscess with obstruction, a surgical consultation was obtained. The consultant could find no convincing evidence of intra-abdominal asbcess or obstruction and believed that distention was caused by paralytic ileus.

The temperature rose to 39°c. after admission and remained elevated; hypotension with blood pressure of 90/60 mm. Hg occurred within ten hours of admission. Intermittent doses of Vasoxyl® were given; on the second hospital day, because of hypotension and low serum sodium, hydrocortisone was given intravenously in the dose of 100 mg. per day. Novobiocin therapy was discontinued and vancomycin was given intravenously 1,500 mg./day. Sodium cycle exchange resins were given rectally.

The fluid intake was maintained at 500 ml. per day, the urinary output was 15 ml. on the second hospital day. The patient remained hypotensive while receiving pressor agents. On the third hospital day he became afebrile, remained confused and exhibited generalized twitching. Hypotension persisted and norepinephrine therapy was begun. An additional 1,500 ml. fluid, approximating extracellular fluid in composition was given, Dilantin® therapy was begun, and extracorporeal dialysis was performed over a four-hour period. There was no objective change in his status after dialysis. On the fourth hospital day hypotension persisted, and a tracheostomy was performed to facilitate removal of tracheobronchial secretions. Examination of the urine on three occasions revealed hyaline and granular casts, some of which were broad and contained red blood cells. Increasing numbers of red blood cells were noted on successive days. A urine osmolality was 380 mOsm per L., on one occasion, 420 mOsm per L. on another. A renal biopsy was planned in order to clarify the diagnosis. This was scheduled for the fifth hospital day, but in the early morning of that day the temperature, which had remained below 38°c., spiked to 39°c. and a large quantity of tracheal secretions was noted. Despite suctioning and pressor therapy, respirations and cardiac action ceased about three hours after the spike in temperature; efforts to resuscitate the patient, including thoracotomy and cardiac massage were unsuccessful.

CLINICAL DISCUSSION

DR. SOL SHERRY: The patient was a fifty-two year old man who was in good health except for recurrent pain in the lower part of his back due to a herniated disc. Since conservative measures did not give him relief, laminectomy was advised. Shortly after this elective and supposedly clean surgery, a wound infection and septicemia developed due to a hemolytic Staph. aureus. Drainage of the infected wound and administration of large amounts of antibiotics, based on sensitivity tests, appeared to bring the systemic infection slowly under control. However, a few weeks later the systemic infection flared again and was followed by acute renal failure. On admission to Barnes Hospital the patient was septic with evidence of renal failure. Despite heroic measures, he rapidly succumbed to his illness. This case should serve well to emphasize the staphylococcal problem and its serious nature. In addition, we have an intriguing problem concerning the cause of the acute renal failure. Dr. Harford, would you begin the discussion by telling us how serious is the problem of staphylococcal bacteremia?

DR. CARL HARFORD: Information concerning the seriousness of the problem of staphylococcal infection is not easy to obtain, but I think that the recent figures reported by Finland and his co-workers* are very revealing. This is a particularly good study for two reasons. One is that Dr. Finland and his associates have been carrying out careful cultures in the same hospital over a period of many years. Secondly, it is probable that the positive cultures are significant because the organisms were cultivated from body fluids or cavities that do not normally contain bacteria. The figures of certain years were presented for the following reasons: 1935 represented the era before sulfonamides; by 1941, sulfonamides had been in use for a significant period of time; by 1947, penicillin had been used extensively; by 1951, broad spectrum antibiotics had come into use. The years 1953, 1955 and 1957 were included to indicate recent experience.

Some of the findings follow. In recent years the incidence of pneumococcal bacteremia has fallen off, but the incidence of staphylococcal bacteremia has been quite different. Presence of staphylococci in blood cultures decreased in frequency after penicillin was used, but lately the incidence of staphylococcal bacteremia has shown a striking increase, and is much greater

* FINLAND, M., JONES, W. F., JR. and BARNES, M. W. Occurrence of serious bacterial infections since introduction of antibacterial agents. *J. A. M. A.*, 170: 2188, 1959.

than it was during the periods before or just after the introduction of the sulfonamides. The number of patients dying with pneumococcal bacteremia has declined markedly, but the number of patients dying with staphylococci in the blood has increased greatly. Another significant aspect of the study is that the recent increase in bacteremia is not only of staphylococci, but also of gram negative bacilli such as proteus, pseudomonas and aerobacter. With these organisms also, there has been a great increase in frequency of bacteremia, and a similar increase in the number of patients dying with these organisms in the blood.

In my opinion, the problem of staphylococcal bacteremia is greater now than it was before the introduction of antibiotics.

DR. SHERRY: It is interesting to note that in most large series, the incidence of staphylococcal sepsis is highest following surgery, or in patients with serious underlying disease. Certain surgical procedures seem to predispose more commonly to staphylococcal sepsis than others. For example, in the experience of the Mayo Clinic transurethral resection ranked first, and laminectomy for herniated disc second. Dr. Cole, can you explain this high incidence following surgery, and why the incidence is higher following certain surgical procedures?

DR. WILLIAM ROBERT COLE: I think the development of sepsis in general, and staphylococcal sepsis in particular, must be related to the organism which the patient contacts, the virulence of that organism, the size of its inoculum, and the patient's ability to resist infection. In general, postoperative surgical patients have a lowered local and general resistance because of the recent anesthetic, the surgical wound, and frequently the presence of indwelling catheters and tubes. For these reasons a postoperative surgical patient is in general vulnerable to infection. So far as the predilection of a particular type of wound to infection is concerned, the establishment of a wound infection is related to the quantity of inoculum, the virulence of the inoculum, and the host's resistance. Given an inoculum of staphylococcus into a surgical wound, the wound may or may not become infected, depending upon the local resistance of the tissues in that wound. These local factors may depend upon the patient's general state of health, as well as upon the technic with which the surgeon has handled the wound. The surgeon's technic includes his handling of tissue, the preservation of the viability of tissue and the removal of all foreign body from the wound. Certain wounds, such as that incurred by the transurethral resection of the prostate, receive a large inoculum of organisms, because of the unavoidable local contamination due to the presence of contaminated urine. Wounds, such as the laminectomy wound, present a problem in hemostasis first because of the presence of an open marrow cavity, which tends to bleed freely, and second because of the necessity to detach a large amount of muscle from its insertion to the spinal column. Complete control of minor bleeding in divided muscle is often difficult to achieve. All these problems help to explain a high incidence of infection in certain types of wounds.

DR. SHERRY: Since therapy is often unsatisfactory, prevention of infection becomes of paramount importance. Do you believe that our aseptic technics have suffered and, as a result, this problem is becoming more frequent?

DR. COLE: I think that undoubtedly during the early period of chemotherapy aseptic and antiseptic technics were relaxed. Now we have come to a rude awakening, and there has been a reeducation among surgeons as to the necessity of using strict aseptic technic. The wound infection rates in many institutions can now be favorably compared with those prior to the advent of antibiotics. The seriousness of the infections when they occur may, however, be much greater at the present time than prior to the antibiotic period due to the type of organism which we are encountering.

DR. SHERRY: The mortality from staphylococcal sepsis still remains high despite modern antibiotic therapy. At the Cincinnati General Hospital, the mortality rate from this disease from 1940 to 1947 was 83 per cent, despite therapy with sulfonamides and penicillin. From 1948 to 1958, even with several newer antibiotics and *in vitro* sensitivity tests, the mortality rate still averaged 62 per cent. The cause of this high mortality rate is still unclear. Probably a number of factors contribute; some relating to the host, and some to the biological characteristics of the staphylococcal infection. We recognize the increased incidence of staphylococcal septicemia among seriously ill patients, particularly those whose immune mechanisms have been suppressed by steroids, radiation or other

agents. However, these factors do not exist in our patient, or in many of the patients who have died following surgical procedures. For this reason, much attention is being paid to the peculiar biological characteristics of the staphylococcus. There is an increasing awareness of the high incidence of infection with organisms initially resistant to certain popular antibiotics, and the fairly rapid development of resistance to antibiotics during therapy. However, even this factor did not seem to play a major role in our case. Dr. King, would you comment on the characteristics of the staphylococcus which may seriously limit the effectiveness of our therapy?

Dr. M. Kenton King: We know that some staphylococci produce a powerful necrotizing exotoxin which will destroy tissue, but this factor is difficult to evaluate because strains of staphylococci not possessing this exotoxin produce abscesses equally well. Staphylococci are also known to produce a substance which has been labeled leukocidin, because it destroys leukocytes, although again those strains not possessing this substance certainly produce serious disease. The presence of staphylococcal coagulase does correlate rather well with pathogenicity, and there is evidence that organisms capable of producing this enzyme do resist phagocytosis somewhat better than others.

In recent years, experiments have been carried out by Dr. David Rogers, Professor of Medicine at Vanderbilt, which have attracted much attention. Beginning in 1952, he and Tompsett demonstrated that staphylococci are much more readily ingested *in vitro* by human leukocytes than are pneumococci or streptococci. They further showed that these staphylococci were able to multiply within the polymorphonuclear leukocyte, and eventually to escape after death and lysis of the polymorphonuclear leukocyte. Staphylococci, thought not to be pathogenic, were not able to survive within the leukocyte in this manner. A few years later Rogers demonstrated that in experimental staphylococcal bacteremia, there is a rapid disappearance of staphylococci from the bloodstream during the first ten or fifteen minutes accompanied by a profound leukopenia. Subsequently a chronic long-term low-grade bacteremia persists. Finally, Rogers and others have demonstrated that staphylococci within polymorphonuclear leukocytes, or within walled-off abscesses, are less affected by the administration of antibacterial agents. These workers have some evidence that this is due to the slower metabolism of the organisms under these conditions.

Dr. Sherry: The resistance of staphylococcal infections to chemotherapy then, in large part may be due, to the rapid development of abscesses and the possible survival of the organism within leukocytes and perhaps other tissue cells?

Dr. King: Yes.

Dr. Sherry: Dr. Margulis, would you show us the roentgenograms of this patient?

Dr. Alexander R. Margulis: An abdominal film taken early after admission was interpreted as showing paralytic ileus. Paralytic ileus of this type is quite non-specific.

Because it was clinically believed that this patient had an obstruction of the colon, a barium enema was performed. The colon was seen to be grossly dilated, but no obstruction was encountered.

A left retrograde pyelogram was also obtained. The kidney was normal in size. There was no evidence of separation of calyces or evidence of necrotizing papillitis. It should be pointed out that a kidney may be riddled with small abscesses without any radiographic change.

A roentgenogram of the chest was also taken. In the left lung two rounded lesions containing air and probably representing abscesses surrounded by pneumonitis were seen. The left diaphragm was elevated, and there was a minimal pleural effusion. In conclusion, this patient had a paralytic ileus and multiple abscesses in his left lung.

Dr. Sherry: Dr. Harford, do you have any comments concerning the nature of the infection in our patient or the therapy which may have hampered his response?

Dr. Harford: As you have indicated, the initial progress appeared to be reasonably good, but the patient had bacteremia, and we have to suspect metastatic abscesses in any patient with staphylococcal bacteremia. The lesions that Dr. Margulis has just described could be some; there may be others. There is no reason to believe that the therapy the patient received was eradicative so that it is not surprising that the infection recurred and that this time it was extensive and difficult to control. One of the questions that arises is whether drug-resistant mutants were responsible for the recurrence. Our data, although not what we should like to have, indicate that this may have happened. Such a phenomenon is usually con-

sidered to be uncommon, but it has been described.

DR. SHERRY: Dr. Cole, do you believe that a septic focus persisted in the surgical wound?

DR. COLE: From the description of the wound and the way it was handled in the protocol I would suspect that the wound was healing uneventfully at the time of death. This is not necessarily so, however, for it might be difficult to detect a residual abscess associated with osteomyelitis of the vertebra, which was partially removed, deep in the recesses of this granulating wound.

DR. KING: Are we discussing all aspects of this patient's therapy at this point?

DR. SHERRY: Yes, would you like to comment on it?

DR. KING: I think that patients with staphylococcal bacteremia due to an organism resistant to penicillin from the beginning, as this one was, should be given vancomycin from the outset.

DR. HARFORD: I think this suggestion has real merit. We have figures on the sensitivities of staphylococci isolated in this hospital from infected patients and approximately 70 per cent are resistant to penicillin. With the other antibiotics, except vancomycin and some of the other new ones, there are various percentages of resistance. We have found only one staphylococcus that was resistant to vancomycin. Also, since vancomycin is a bactericidal drug, it does seem to me that vancomycin may be used advantageously in serious situations, e.g., in patients with bacteremia.

DR. SHERRY: Let us now consider the disseminated lesions which this patient may have had. There is evidence that he had multiple abscesses in the lung. In addition, the patient had considerable abdominal distention presumably due to ileus. Dr. Karl, do you believe he had peritonitis?

DR. MICHAEL KARL: I think that his paralytic ileus was merely a reflection of his general toxemia, and I would not expect to find any important intra-abdominal disease.

DR. SHERRY: How did you interpret the abnormal results of the hepatic function tests?

DR. KARL: This patient had a history of heavy alcoholic ingestion, and it is possible that the abnormal results of liver function tests might represent early alcoholic cirrhosis, entirely apart from his present disease. On the other hand, other events concomitant with his disease could explain these abnormal liver functions. He was in shock, both before his transfer here and during his transfer, and it is possible that his liver may show areas of widespread centrilobular necrosis.

DR. SHERRY: Can similar changes be produced by the toxemia associated with sepsis?

DR. KARL: Yes, this can be seen also with overwhelming toxemia. It is possible that the liver may show toxic changes from multiple pulmonary infarcts. There are a number of explanations for the abnormal results of liver function tests.

DR. SHERRY: One of the more serious events in staphylococcal sepsis is the development of a bacterial endocarditis. Dr. Parker, do you believe this patient had a bacterial endocarditis?

DR. BRETT PARKER: I do not think there is much evidence that he did. Although a soft systolic murmur did develop; the patient had a fever and was quite anemic at the time, so perhaps we have a good explanation for the murmur. The film showed normal heart size, and I really believe that there is little evidence of cardiac involvement in general.

DR. SHERRY: Then we only have evidence for the presence of lung abscesses. I am sure Dr. Harford would disagree with this interpretation and would suspect that this man had disseminated abscesses in multiple organs.

DR. HARFORD: Yes, I would. We also have had an experience with a patient who had a staphylococcal infection in the lumbar region with bacteremia which followed lumbar punctures and myelography. At a time when the patient was recovering, small numbers of bacteria persisted in the blood and there was a low grade fever. There were absolutely no clinical signs of infection in the lumbar region, such as tenderness, and yet on laminectomy there was a great deal of extradural exudate. I am impressed by the amount of infection that can exist even near the surface without clinical signs.

DR. SHERRY: Then you would suggest that it may be difficult to detect the presence of multiple abscesses in many organs since they may not produce significant signs or functional alteration, and that we should suspect that our patient will have abscesses in a number of organs other than his lungs.

Now let us consider what other effects we can attribute to the septic state. Our patient had rather interesting electrolyte abnormalities: hyperkalemia, hyponatremia and hypochloremia. The presence of early renal failure may

have been responsible for these changes, and the presence of hypotension raised the possibility of adrenal insufficiency. Dr. Daughaday, can electrolyte changes of the type described occur in septic patients without invoking any other explanation?

DR. WILLIAM DAUGHADAY: Maintenance of the high differential of sodium to potassium across the cell membrane, that is a high extracellular sodium and a low intracellular sodium, and vice versa for potassium, is dependent on the vital processes of the cell. Almost any condition, severe anoxia or severe toxicity of a number of types, will break down this differential and lead to the depletion picture, as Dr. Francis Moore calls it, in which you have a relatively low cellular potassium. For this reason when dealing with a profoundly ill patient it is extraordinarily difficult to use the serum levels of sodium and potassium as a differential diagnostic point. In most cases, as in this case, when faced with the combination of electrolyte disturbances and difficulty in maintaining blood pressure, steroids are used to be on the safe side. Only rarely, however, does postmortem examination give real evidence that adrenal insufficiency was also present.

DR. SHERRY: Are there any studies on the levels of circulating adrenal steroids in patients with severe infections?

DR. DAUGHADAY: Many careful studies have been made particularly in Dr. Spink's laboratory in Minneapolis where they have studied the circulating blood steroids in subjects who have endotoxic shock. In experimental animals and in patients, almost without exception, the blood steroids are high. This is true not only because of adrenal hyperactivity, but also because there is a decrease in removal of steroids from the blood.

DR. SHERRY: Let us discuss the renal problem. The evidence suggests that renal failure was not due to pre- or postrenal factors, but rather to renal disease *per se*. Since acute renal failure is a fairly unusual event in staphylococcal septicemia uncomplicated by shock, its presence in this case, in which there is no history of shock before admission to Barnes Hospital, raises for consideration several different types of renal disease. Those I would consider as the more likely possibilities include acute tubular necrosis, bilateral cortical necrosis and severe pyelonephritis with multiple abscesses. Those which I would consider as less likely in our patient include necrotizing papillitis, acute glomerulonephritis, hypersensitivity angiitis, the diffuse nephritis seen with bacterial endocarditis, radiation nephritis and bilateral renal vein thrombosis, renal artery occlusion or embolization. Dr. Bricker, would you agree with this appraisal?

DR. NEAL BRICKER: Yes, I would agree that the list covers the major possibilities. In an attempt to arrive at a specific etiologic diagnosis, I think one of the important considerations is the date of onset of the lesion. That the disease was not of long duration seems fairly well established in view of the fact that in March 1959 the patient's urine sediment was negative, and on admission to the hospital prior to surgery, the blood urea nitrogen was reported as normal. On the third day following surgery, the urine contained protein and casts; however, at this time the patient had a high fever and on the twenty-seventh day following surgery the urine sediment again was negative except for a trace of protein which again could be attributed to fever. I think, therefore, that it is reasonable to assume that prior to the twenty-seventh day, he had no significant parenchymal lesion in his kidneys. On the fifty-second day he was noted to be oliguric, and the next day his blood urea nitrogen was recorded as 80 mg. per cent. Hence, the onset of the renal disease must have occurred sometime between the twenty-seventh and fifty-second postoperative day; probably closer to the latter. If this is true, the underlying renal lesion must be classified as an acute process which progressed rapidly and resulted in death in a period of approximately ten days.

DR. SHERRY: Do you believe that the presence of red cell casts might be more in favor of some type of glomerular disease?

DR. BRICKER: From a statistical point of view, in a patient with an acute febrile illness with overwhelming constitutional manifestations and at least two episodes of hypotension, acute tubular necrosis would be the most likely diagnosis. However, the red cell casts, as well as several other factors, do not support this diagnosis.

DR. SHERRY: Before we discuss them, let us consider further the possibility of acute glomerulonephritis. This patient had a staphylococcal infection rather than a streptococcal infection. Dr. Morrin, does acute glomerulonephritis occur following bacterial infections which are not streptococcal in origin?

DR. PETER MORRIN: Most of the recent evidence shows that about 80 per cent of cases

of acute glomerulonephritis are due to streptococcus. This leaves about 20 per cent which have to be explained by other causes. In the literature many different etiologies are given, but often without adequate bacteriologic or serologic documentation to exclude a streptococcal infection. Pneumonococci, viruses, rickettsia, the malaria protozoa and other organisms have been implicated. There was a recent well documented study by Bates, Jennings and Earle of ten cases in which they definitely ruled out streptococci and were unable to implicate any other bacteriologic agent. In regard to staphylococci as a possible cause of proliferative glomerulonephritis, I have been unable to find any report of this in the literature. Bell states categorically that it does not occur. However, he did describe three cases of severe staphylococcal infection in his series, which were associated with what he called an exudative glomerulonephritis in which the glomerular capillaries were filled with leukocytes, and he stated that the borderline between this and staphylococcal infection of the kidney was rather nebulous.

DR. SHERRY: On Bell's statement, we shall exclude glomerulonephritis from further consideration. We had no radiographic evidence to support a necrotizing papillitis. Hypersensitivity angiitis certainly would have to be considered in a subject with a severe infection treated with multiple antibiotics. However, sulfonamides were not used, and there was no hypertension. Admittedly this is not strong evidence against the diagnosis, but there is little to support it. The diffuse nephritis of bacterial endocarditis can be rapid in onset and can lead to uremia; multiple types of lesions are observed in the kidney. However, we have no evidence for a bacterial endocarditis in this patient. Since there is little to suggest a sudden bilateral vascular occlusive disease, we are left with acute tubular necrosis, bilateral cortical necrosis or severe pyelonephritis. Dr. Nickel, of these three, which would you favor?

DR. JAMES NICKEL: I think it is difficult to choose from among these three because we are lacking clinical information that would be helpful. However, the entire picture is one of overwhelming infection, and I would be inclined to exclude a typical acute tubular necrosis. This leaves the possibility of either the cortical necrosis or pyelonephritis. I find it difficult to choose between these two, and it would really be a guess. I think that this is most likely an acute cortical necrosis, although we certainly may find multiple abscesses in the kidney.

DR. SHERRY: Does bilateral cortical necrosis occur with septicemia?

DR. NICKEL: Yes, it certainly can.

DR. SHERRY: Although bilateral cortical necrosis is a rare entity, when it occurs in males, it is most often associated with a septic process. Dr. Karl, do you believe that acute tubular necrosis is the more likely diagnosis in this case?

DR. KARL: No, we were impressed by the fact that this man had an overwhelming septicemia, and we were inclined to think of bilateral cortical necrosis or multiple abscesses; statistically I think we would lean towards multiple abscesses throughout both kidneys.

DR. SHERRY: How often does severe infection of the kidneys occurring during the course of staphylococcal septicemia produce renal failure?

DR. KARL: It is a focal process, and as a rule does not cause renal failure to this degree. One would expect a more diffuse process to accomplish this sort of renal failure.

DR. SHERRY: Dr. Bricker, would you summarize your views about this patient's renal disease? I know you were concerned about accepting the diagnosis of acute tubular necrosis, although on a statistical basis this might be most commonly encountered in association with acute renal failure.

DR. BRICKER: Very briefly there are four points against acute tubular necrosis. First, we have no known precipitating event which bears an appropriate temporal relationship to the apparent onset of the disease. Second, the protocol records a period of total anuria, a phenomenon which is extremely unusual in acute tubular necrosis. Third, there were red cell casts, a finding which is also unusual in acute tubular necrosis. And finally, the urinary osmolality, measured on two occasions, was 380 and 420 mOsm/kg. H_2O, respectively. Unfortunately, no value is available for the plasma osmolality. However, if one subtracts the urea osmols from this, the patient was hyponatremic, and despite the estimated 40 to 50 mOsm./kg. contributed by urea and other retained solutes, one is left with the conclusion that the urine was distinctly hypertonic to the plasma. This is so rare in acute tubular necrosis as to make one seriously question the diagnosis. I would also rule out multiple abscesses because of the fact that this was a diffuse disease which

must have involved virtually every nephron, and it would take an enormous number of abscesses. Finally, I am unable either to rule in or out the diagnosis of bilateral cortical necrosis.

DR. HARFORD: I think that if the staphylococcal infection of the kidney was severe enough to cause renal failure we would have found many staphylococci in the urine.

DR. SHERRY: That is a good point. Dr. Orlowski, do you have a choice between bilateral cortical necrosis and acute tubular necrosis?

DR. THADEUS ORLOWSKI: Yes. I would favor acute tubular necrosis for these reasons. First, because on the first day of his illness the patient voided about 210 cc. of urine, which is rare in acute bilateral cortical necrosis. Second, the patient with bilateral cortical necrosis often has frank hematuria. Third, the volume of urine increased very quickly. On June 14, it was only 6 ml., and on June 18 it was 50 ml. This is against bilateral cortical necrosis.

DR. SHERRY: The fact that the urine volume increased would be a point against bilateral cortical necrosis, but we have seen patients whose urine volume has slowly and progressively increased with bilateral cortical necrosis.

DR. ORLOWSKI: Yes, but this ordinarily occurs over a period of several weeks. It is difficult to find the cause of acute tubular necrosis in this case. However, it is known that injection of staphylococcal endotoxin causes renal ischemia and paralytic ileus, too. It is possible that there was some degree of ischemia due to the infection. My diagnosis, therefore, would be acute tubular necrosis.

DR. SHERRY: One of the experimental methods for producing cortical necrosis is to inject staphylococci or staphylococcal toxins into the circulation; however, as you point out, if enough shock is produced, acute tubular necrosis may develop. Dr. Kime, our patient received radiation to his back a few days before the appearance of renal failure. Is there any possibility that radiation nephritis may have been responsible for his renal failure?

DR. W. KIME: The quickest and most effective way in which the subject of radiation nephritis can be covered is to consider the diagnosis as it might be applied to this man. Radiation nephritis is an established clinical entity, but the clinical data are inconsistent with the diagnosis in this case for the following reasons. First, the latent period between the administration of the radiation and the onset of the renal disease is much too short. In Luxton's* series, probably the largest recorded in the literature, the shortest latent period was three months, and the average was six to twelve months. This man showed oliguria one day after receiving radiation. The second point against radiation nephritis is the dosage. In all the cases reported in the literature, at least 3,000 r were administered. This man received approximately 1,500, admittedly over a shorter period of time than usual. Third, the course is against the diagnosis; most cases of radiation nephritis, even the acute ones, do not end in death before ten weeks. This man died one week after the onset of his disease.

DR. SHERRY: I agree completely, but it should be recognized that large amounts of radiation to the renal area can produce a chronic nephritis slowly progressing to uremia.

We shall offer as our final diagnosis: staphylococcal septicemia secondary to an infected laminectomy wound; multiple disseminated abscesses; and acute renal failure possibly due to acute tubular necrosis or bilateral cortical necrosis.

PATHOLOGIC DISCUSSION

DR. ATSYO MIKATA: At autopsy the body appeared well developed and well nourished, weighing 80 kg. The skin, sclera and mucous membrane were icteric, and on the back over the lower lumbar area there was a wide scar of the previous operation. There were also evidences of the recent tracheotomy and the thoracotomy for cardiac massage.

The lungs were congested and edematous, with multiple small abscesses, especially frequent in the upper lobe of the left lung. Several small, triangular, firm areas of severe congestion, typical of recent infarcts, were found subpleurally. The heart was slightly hypertrophied and dilated, weighing 485 gm., but the most spectacular findings were on the tricuspid valve. Huge, friable vegetations, the largest measuring 2 by 2.5 by 2.5 cm., were rather firmly attached to the leaflets of the tricuspid valve. (Fig. 1.) The valve was otherwise normal, as was the remainder of the heart. The kidneys were enlarged, weighing 310 and 312 gm., respectively, and were very pale. The capsule was difficult to remove, and on the cut surface the parenchyma was yellow and the cortex slightly swollen. The medulla was also pale, but the cortico-

* LUXTON, R. W. Radiation nephritis. *Quart. J. Med.*, 22: 215, 1953.

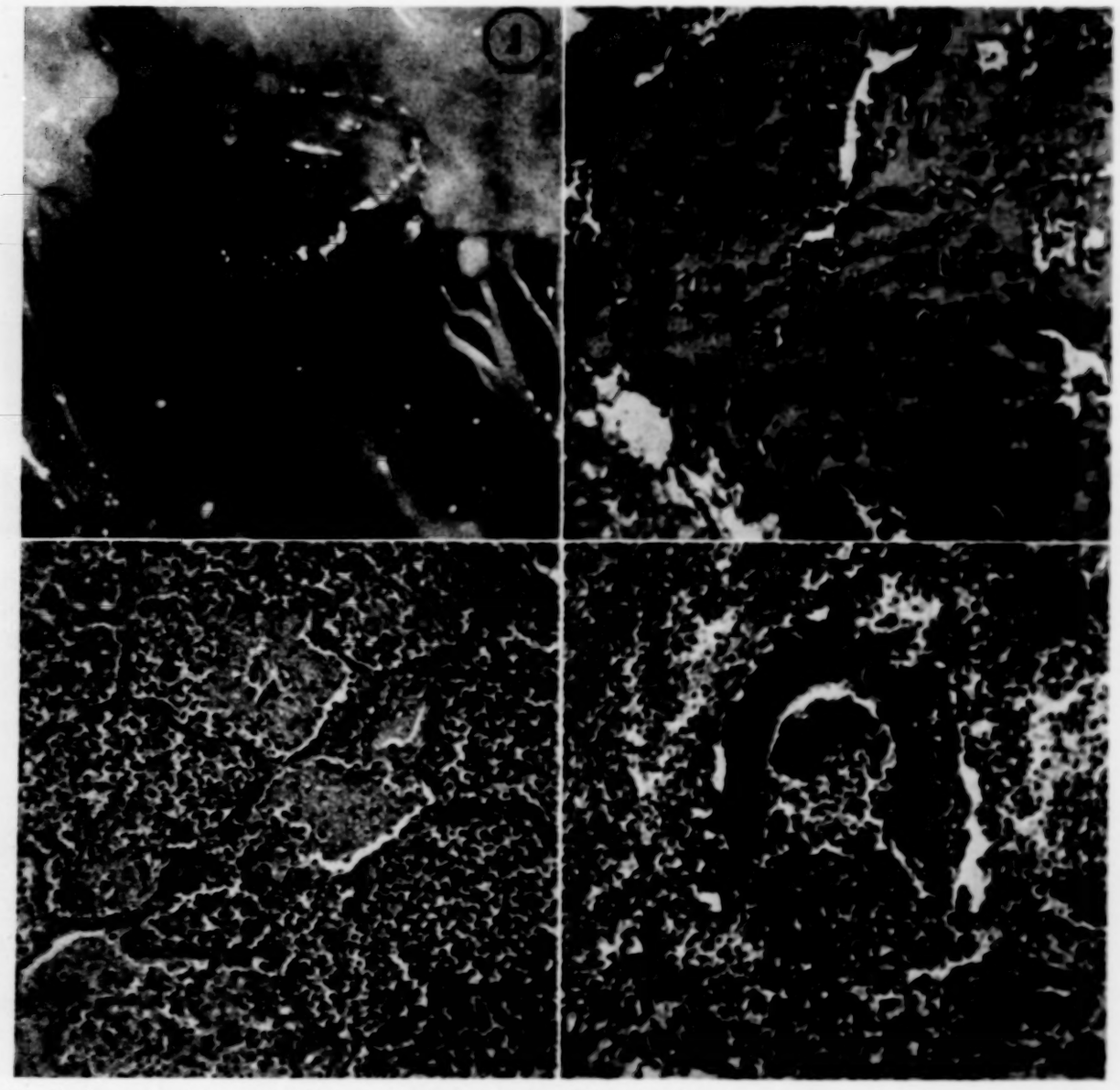

FIG. 1. Close-up of the gross lesion on the tricuspid valve. This polypoid mass was the largest of several vegetations present.

FIG. 2. Clumps of bacteria in the fibrin vegetation in Figure 1. Hematoxylin and eosin × 100.

FIG. 3. Consolidation of the lung by fibrin and polymorphonuclear leukocytes. Many gram positive cocci and some gram negative rods were found in such areas. Hematoxylin and eosin × 100.

FIG. 4. A necrotic focus in the lung containing a clump of staphylococci in its center. This is the result of embolization of a fragment of the bacterial vegetation on the tricuspid valve. Hematoxylin and eosin × 100.

medullary junction was a bit exaggerated. The liver weighed 2,700 gm. and was yellow. No abscesses were found outside the lungs. The remainder of the autopsy was within normal limits.

DR. ROBERT M. O'NEAL: The bacterial vegetations on the tricuspid valve (Fig. 2), shown grossly in Figure 1, were composed of large clumps of staphylococci in a fibrinous mesh, characteristic of staphylococcic endocarditis. (Fig. 2.) In the lungs there were areas of confluent pneumonia with polymorphonuclear leukocytes and fibrin filling the air spaces. (Fig. 3.) On bacterial stain of these areas there were

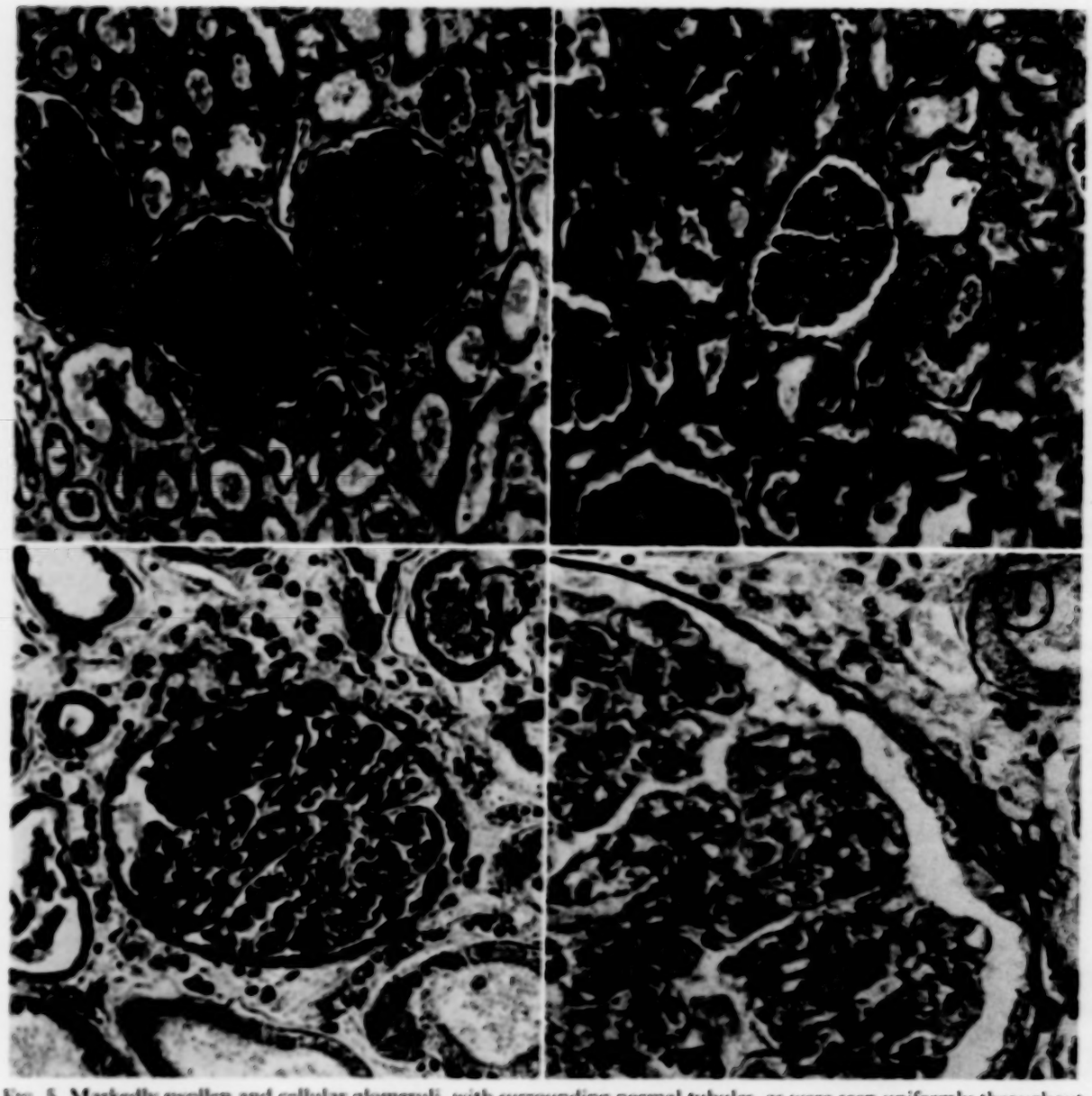

FIG. 5. Markedly swollen and cellular glomeruli, with surrounding normal tubules, as were seen uniformly throughout both kidneys. Hematoxylin and eosin × 100.

FIG. 6. Glomerulus from a kidney of a man of the same age as the patient but without renal disease, for comparison with Figure 5. Hematoxylin and eosin × 100.

FIG. 7. A fibrin thrombus in a glomerular capillary loop. These thrombi were rare. Hematoxylin and eosin × 200.

FIG. 8. Higher magnification of a glomerulus to demonstrate the lack of epithelial proliferation in Bowman's space and the marked endothelial proliferation within glomerular capillaries. Periodic acid-Schiff stain × 420.

numerous gram positive cocci, some in short chains, and occasional gram negative bacilli. These cocci were not arranged in clumps as we expect of staphylococci, although we did culture Staph. aureus from the lungs at postmortem. It is possible that organisms other than that cultured played some part in the pneumonia.

In other scattered areas of the lungs we found necrotic foci containing large clumps of staphylococci (Fig. 4) which undoubtedly represented embolic abscesses resulting from fragments of the tricuspid valvular vegetation being carried to the lungs. Some of these emboli had produced small infarcts. The abscesses and infarcts did not

appear to be in relation to the diffuse confluent pneumonia.

On microscopic examination the kidneys had huge glomeruli, as demonstrated by the comparison between glomeruli in this patient (Fig. 5) and those in a man the same age without renal disease. (Fig. 6.) The glomeruli in this case were cellular, and the surrounding tubules were in good condition, with only a few protein casts here and there. There were no polymorphonuclear leukocytes trapped in glomerular capillaries, as was described by Dr. Sherry as occurring in the "exudative" nephritis of bacterial endocarditis. We found an occasional lesion of the type that has been called a "microinfarct" of the glomerulus. These appeared to be small fibrin masses in loops of the glomerular capillaries (Fig. 7) but these were rare. Because the bacterial vegetation was on the tricuspid valve, most of the small particles that might have embolized to the glomeruli were trapped in the lungs. On high power magnification of periodic acid-Schiff stained sections (Fig. 8), the basement membranes of capillaries appeared intact, not especially thickened, and the epithelium was not prominent. The cells that proliferated in the glomeruli were the endothelial cells, and they practically filled the capillary loops. This is typical of an early stage of acute "proliferative" glomerulonephritis.

The glomerular disease, acute proliferative glomerulonephritis, is of the type that, if less severe, might have eventually progressed into the usual, classic type of chronic glomerulonephritis. That this disease developed in the presence of acute staphylococcic endocarditis may have been coincidental, but that would be quite a coincidence. It seems probable that the renal disease resulted, in some way, from the staphylococcal infection, although of course this type of renal disease usually is associated with streptococcal disease.* The infectious disease of the lungs was recent, and therefore an unlikely cause for the glomerular disease.

* BELL, E. T. Renal Diseases, p. 144. Philadelphia, 1947. Lea & Febiger.

No significant vascular disease was present in the kidneys, but some interesting lesions of the papilli were found. There was a small focus of necrosis at the tip of a papillus, in which the periodic acid-Schiff stain revealed numerous, branching, segmented hyphae of monilia. This monilia might have been introduced at the time of ureteral catheterization because it was present only on and near the surface of the papillus, and there was no other evidence of moniliasis found at autopsy. In the collecting tubules there were many granular casts but with the marked glomerular disease that this patient had, acute tubular necrosis can easily be eliminated as the cause of anuria.

I should comment on a few of the questions raised in the clinical discussion. Microscopically, the liver was essentially normal and we have no explanation for the jaundice other than the ones mentioned by the discussants: the small pulmonary infarcts, the hemolysis due to septicemia, and the possible effect of toxemia on the liver. There was no evidence of adrenal disease. We cannot tell you definitely whether or not there was still some infection remaining in the apparently healed laminectomy wound, but at least the bacterial endocarditis offers a ready explanation for the persistent or recurrent septicemia.

Final anatomic diagnoses: Healed incisional wound with wide scar over the lumbar vertebrae (history of laminectomy for herniated nucleus pulposis, April 16, 1959, and postoperative wound infection; Staph. aureus cultured from blood on April 20 and May 21, 1959); tracheotomy wound on the neck; precordial unhealed sutured wound (15.5 cm.) and ecchymoses of epicardium (history of cardiac resuscitation); acute bacterial endocarditis of the tricuspid valve (history of Staph. aureus septicemia); advanced acute confluent pneumonia with multiple abscesses and infected infarcts (Aerobacter and Staph. aureus cultured at autopsy); microabscess in the heart; acute glomerulonephritis; uremic pancreatitis, advanced; jaundice, moderate; hemorrhagic cystitis, moderate; and moniliasis of renal papillae.

Case Reports

Carcinoma of the Parathyroid Gland with Pulmonary Metastases and Cardiac Death*

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Carcinoma of the parathyroid gland is a rare disease. Its exact incidence is difficult to determine from the literature because of the differing criteria that various authors use in making the diagnosis. This point is readily appreciated when one consults the reviews on this disease that have been published [*1–5*]. In the most recent of these, Black [*5*] reviewed the literature on parathyroid carcinoma to the end of 1953. Using the criteria of endocrine hyperfunction and local tissue invasiveness or metastasis, Black accepted the diagnosis in twenty cases. Using the same criteria it would appear that another eight cases have been described since that time [*6–11*], making a total of twenty-eight. Only eight cases of parathyroid carcinoma with *visceral* metastases have been reported [*6,8,12–17*]. The metastases have been chiefly to the lungs and liver, but invasion of the kidneys, pancreas, spine, ribs and adrenals also has been noted. In this report we wish to describe what is probably the ninth patient with visceral metastases.

CASE REPORT

The patient (Mrs. M. H.), who was twenty years old, had a total of four admissions to the Toronto Western Hospital. During the first admission, from March 25 to April 23, 1953, she stated that she never had had much ambition or energy and had always been known to be fairly nervous. In October 1952 she had first noted tenderness in the lateral aspect of her left calf. Two weeks later the left leg had felt weak. By December the pain had shifted to the left thigh and from there to both iliac crests. The patient stated that she was reasonably well on arising in the morning but noted progressive weakness during the day. She denied dyspnea or chest pain. She had noted swelling of the ankles premenstrually only in the summer. Her menstrual periods began at the age of thirteen, had an interval of twenty-five days and lasted four or five days; there was no change in the pattern. The patient denied weight loss and mentioned specifically that her appetite was good. She denied polydipsia, polyuria and digestive complaints. Her only significant past illnesses were three fractures of the left arm, between the ages of thirteen and fourteen, concerning which there was no helpful information; and an episode of vomiting which occurred three years prior to admission, lasted three months and was attributed to nerves. Roentgenograms and biochemistry tests were obtained in Sudbury, Ontario by Dr. D. Myatt who referred the patient to one of us (W. H. B.) with the diagnosis of hyperparathyroidism.

On examination the patient appeared well nourished and cheerful. Her weight was 103 pounds. There was slight, diffuse enlargement of the thyroid gland but no nodules could be felt in the neck. The chest was clear. The heart was of normal size, the blood pressure was 110/60 mm. Hg. A blowing mitral systolic murmur, grade 2 in intensity, was present. Abdominal examination was within normal limits. Neurological examination was entirely normal. There was no obvious hypotonia. The joints were normal. There was some tenderness over the left thigh and the upper medial aspect of the left tibia.

The hemoglobin was 12.8 gm. per cent; white blood count, 13,400 per cu. mm.; the differential cell count was normal. The erythrocyte sedimentation rate (Westergren) was 19 mm. in one hour. Urinalysis revealed a specific gravity of 1.020 and was negative for albumin. Microscopic examination of the urine sediment revealed hyaline, hyaline-cellular and hyaline-granular casts. The maximum specific gravity obtained during the Mosenthal two-hour

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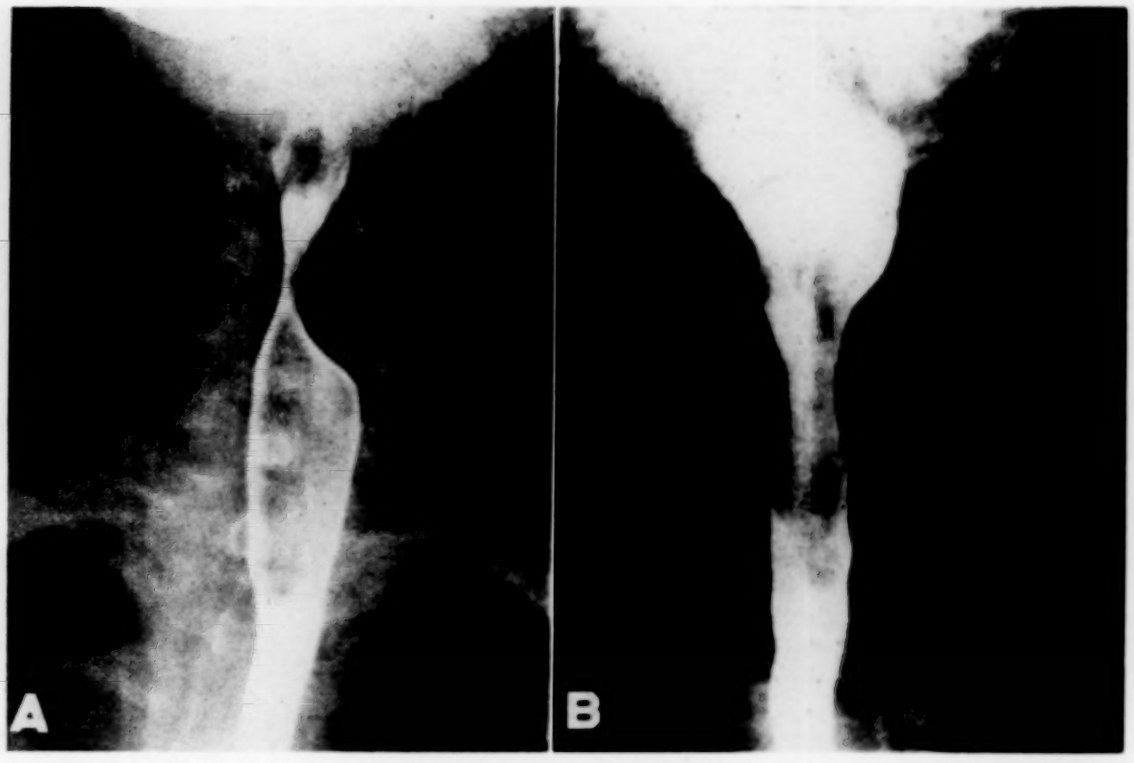

FIG. 1. Barium swallow in the oesophagus. A, preoperative film showing the indentation from the left. B, postoperative film showing the disappearance of the indentation and return to normal configuration.

kidney function test was 1.020. On a 100 mg. calcium diet, she excreted 593, 390 and 315 mg. of calcium in three consecutive twenty-four-hour urine specimens. The blood biochemistry findings are shown in Table 1. The serum proteins were normal.

Barium swallow showed a defect in the barium column on the left, just above the level of the cricopharyngeus. (Fig. 1A.) A chest roentgenogram disclosed no abnormalities. All the bony structures examined showed demineralization which was particularly marked in the femurs and tibias, in the skull and in the lower dorsal and lumbar vertebras. Cystic areas of rarefaction were recognized in the following locations: Upper end of the left humerus, in the left tibia and fibula (Figs. 2A and B), in the inferior and superior pubic rami, bilaterally (Fig. 3A) and questionably in the left ilium near the sacroiliac joint. A plain film of the abdomen showed nephrocalcinosis of both kidneys but an intravenous pyelogram demonstrated good function with normal appearing calyces, pelves and ureters. In the dental films no lamina dura was seen.

Because of the characteristic blood chemical findings, the hypercalcuria, the indentation in the barium swallow and the characteristic roentgenographic findings, a diagnosis of primary hyperparathyroidism was made. Accordingly, on April 7, 1953, the neck was explored by Dr. R. Laird, who removed a non-adherent tumor from behind the upper pole of the left lobe of the thyroid. The specimen consisted of a well encapsulated, firm, slightly lobulated mass of tissue measuring 3.5 by 2 by 1 cm. and weighing 6.1 gm. The cut surface had a somewhat gelatinous, slightly yellowish appearance. The tumor was composed of fairly uniform chief cells with a few scattered transitional water-clear cells and oxyphil cells. No trabecular arrangement was noted. The cell nuclei were quite uniform with prominent nucleoli. (Fig. 4.) Only one small area showing some pleomorphism of cells and giant nuclei was seen. Scattered areas of necrosis were noted, and one or two areas of capsule invasion.

Postoperatively the patient was treated with calcium lactate supplement, aluminum hydroxide tablets and vitamin D. No tetany developed. A repeat barium swallow (Fig. 1B) was now normal. Two weeks postoperatively, while taking the 100 mg. calcium diet, she excreted only 47 and 59 mg. of calcium in two consecutive twenty-four-hour urine specimens. All her blood chemical findings gradually returned to normal (Table 1), except that her serum alkaline phosphatase was still elevated (97 units) at the time of discharge.

The patient was readmitted for assessment from July 18 until July 22, 1953. Following the operation she had gained 20 pounds and claimed to have regained her vigor. Her bone pains had largely disappeared with the exception of a moderate aching

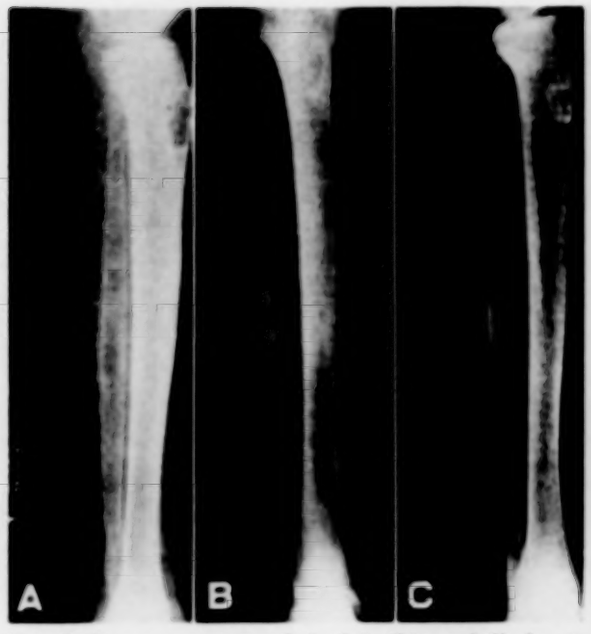

FIG. 2. Roentgenograms of the left tibia and fibula. A, lateral view and B, anteroposterior view taken preoperatively, showing characteristic cysts. C, taken on November 12, 1953, seven months after removal of the tumor, showing distinct recalcification of the cysts.

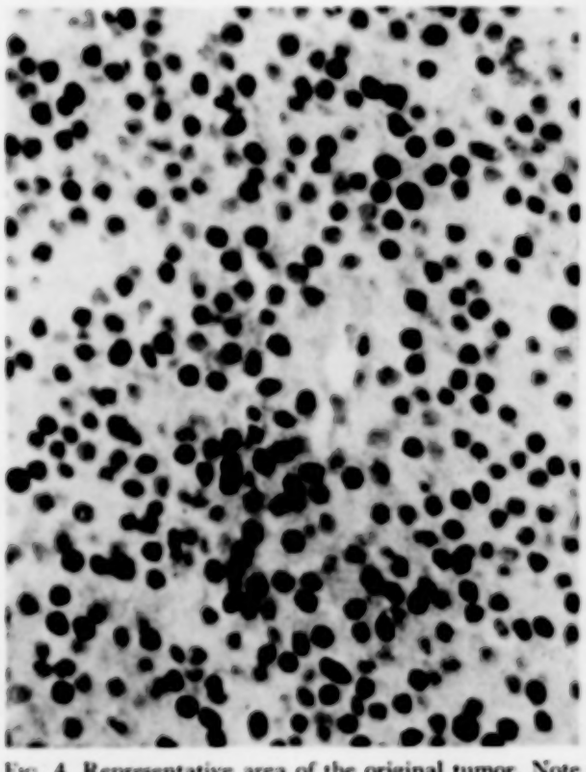

FIG. 4. Representative area of the original tumor. Note the uniformity of the chief cells. Many of the nuclei contain two prominent nucleoli. Hematoxylin and eosin stain, original magnification × 360.

FIG. 3. Anteroposterior view of the pelvis. A, preoperative film showing cysts of the inferior and superior pubic rami, bilaterally. B, film taken on November 12, 1953, seven months postoperatively, showing marked recalcification. C, film taken on February 2, 1955, showing new destruction especially of the right superior ramus.

in the lower part of the back. All other functional enquiry was negative. On examination there was the previously noted enlargement of the thyroid gland. The blood pressure was 145/80 mm. Hg and the heart was normal in size. The blood chemical findings (Table 1) were now practically normal with the exception of a rather high serum phosphorus and minimally elevated alkaline phosphatase. Her hemoglobin was 13.2 gm. per cent; erythrocyte sedimentation rate, 14 mm. and white blood count, 9,300 per cu. mm. The Sulkowitch test for urinary calcium performed on a fasting urine sample was normal. The maximum urinary concentration (two-hour test) was 1.021.

The patient was admitted to the hospital once more, from November 11 to November 19, 1953. At this time she had minimal complaints of fatigue, some aching pain in the left flank, increasing nervousness and palpitations. She had also noted excess perspiration of her hands and feet, which was confirmed on examination. It was further noted that she had occasional runs of tachycardia.

TABLE 1

SUMMARY OF BLOOD CHEMISTRY FINDINGS

Date	Serum			Blood Non-protein Nitrogen (mg. %)	Serum			
	Calcium (mg. %)	Phosphorus (mg. %)	Alkaline Phosphatase (King-Armstrong units)		Sodium (mEq./L.)	Potassium (mEq./L.)	Chloride (mEq./L.)	CO_2 (mEq./L.)
First Admission								
3/30/53	....	...	...	31	139	4.7	103	21
4/1/53	14.9	1.3	188	..	...	...	...	...
4/6/53	13.5	1.9	114	..	...	...	...	...
4/7/53	14.1	1.4	75	..	...	...	...	...
4/7/53 operation	....	...	...	..	...	...	...	...
4/8/53	11.2	1.7	91	..	...	...	...	...
4/9/53	10.6	1.1	37	..	...	...	...	...
4/15/53	11.0	2.7	107	..	...	...	...	...
4/23/53	10.1	3.6	97	..	...	...	...	...
Second Admission								
7/21/53	10.1	5.3	16	42	...	...	...	...
Third Admission								
11/12/53	10.9	3.6	38	28	...	...	...	...
Final Admission								
2/1/55	17.1	3.9	53	39	...	...	...	...
2/3/55	19.1	3.4	60	...	144	3.9	104	20
2/9/55	22.0	4.0	...	..	...	...	...	...
2/10/55 operation (neck)	....	...	...	..	...	...	...	...
2/10/55 12:30 P.M.	19.8	3.8	71	..	...	...	...	...
2/11/55	20.0	4.0	78	42	144	4.1	109	23
2/14/55	20.4	4.1	48	46	...	...	...	...
2/15/55	21.2	5.1	43	..	...	...	...	...
2/16/55	23.4	4.0	44	..	...	...	...	...
2/16/55 operation (mediastinum)	....	...	...	..	...	...	...	...
2/16/55 1:30 P.M.	18.2	6.6	47	..	...	...	...	...
2/17/55	21.2	5.3	29	..	...	...	...	...

Her hemoglobin was 12.9 gm. per cent and the erythrocyte sedimentation rate was 5 mm. The maximum specific gravity of the urine (two-hour test) was 1.026. The only abnormality noted in the blood chemical findings (Table 1) was a high serum alkaline phosphatase of 38 units. Roentgenograms taken on this admission showed evidence of progressive recalcification throughout. The cyst-like areas in the left tibia and fibula showed recalcification (Fig. 2C) but were still visible and those in the pubis (Fig. 3B) showed similar improvement. The appearance of the skull was now considered to be normal. The spine still showed evidence of demineralization but appeared more dense than at the previous examination. The nephrocalcinosis was unchanged.

The patient, now aged twenty-one, was admitted for the last time on January 30, 1955, twenty-two months postoperatively. She had been in her usual health until October 1954 when she noted increasing fatigue and, as the two major complaints, thirst and polyuria. She volunteered the information that she drank one to two quarts of milk and eight to eleven glasses of water daily, and was up two or three times a night passing large volumes of urine. She now had palpitations, morning nausea, occasional vomiting, constipation and some muscle cramps in her left thigh and both legs. She had lost weight and was now back to 105 pounds. Her menstrual periods were unchanged.

On examination she appeared rather tense and gaunt. No masses were felt in the neck and her chest was clear. The blood pressure was 120/75 mm. Hg. The heart was normal in size, the apex rate varied between 110 and 130, the usual systolic murmur was still present. Abdominal examination was within normal limits. Neurologically, her reflexes were brisk and bilaterally symmetrical. There was no bone tenderness. An ophthalmological consultation revealed no evidence of abnormal calcium deposition in either eye by slit-lamp examination.

Her hemoglobin was 11.4 gm. per cent; white count, 13,800 per cu. mm.; and the erythrocyte sedimentation rate, 51 mm. Routine urinalysis showed a specific gravity of 1.013 and a trace of albumin. Microscopic examination revealed 30 to 40 white cells per high power field, with occasional red cells and

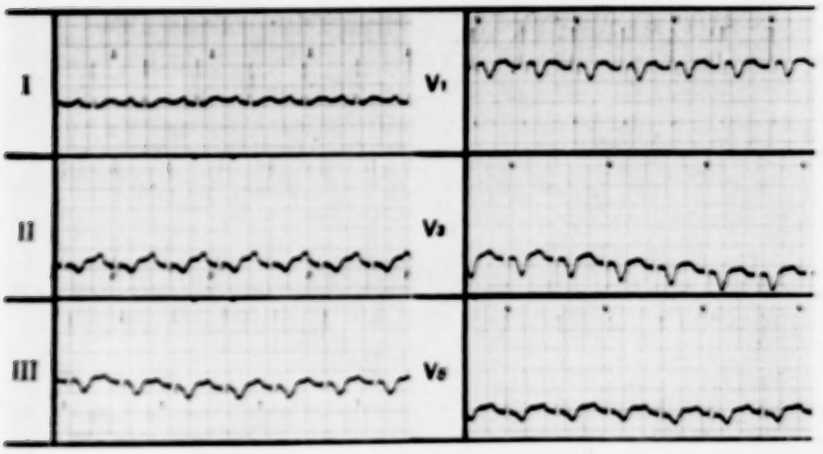

FIG. 5. Electrocardiogram taken on last admission when patient's serum calcium was between 19.1 and 22.0 mg. per cent. See text for description.

a moderate number of granular, hyaline and cellular casts. While ingesting 100 mg. of calcium she excreted a daily average of 858 mg. of calcium over three consecutive days. The serum proteins were normal. The blood chemical findings are shown in Table I. On radiological skeletal survey the bones now showed increased trabecular markings and all appeared demineralized to a considerable degree. The skull in which considerable remineralization had occurred following her operation, now showed more severe rarefaction than ever. There was new and marked destruction of the right superior pubic ramus. (Fig. 3C.) The lesions in the tibias and fibulas were unchanged from the last examination. The nephrocalcinosis appeared to have increased. The chest roentgenogram revealed no abnormality in the lungs or heart. An electrocardiogram (Fig. 5) taken on February 7 when the serum calcium was between 19.1 and 22.0 mg. per cent showed the heart rate to be 118, with regular rhythm and no extrasystoles. However all the T waves except those of lead I were inverted. Furthermore the Q-T interval was slightly shortened, the Q-T$_c$ equalling 0.33 seconds. The P-R interval and the QRS width were normal. There was a "plateauing" of the T wave in lead I. An electroencephalogram obtained on February 4 when her serum calcium was 19.1 mg. per cent was reported by Dr. A. M. Park to reveal a symmetrical dominant rhythm at 11.5 to 13 cycles per second. This was mixed with a good deal of random 4 to 7 cycle per second activity from many regions, often in short runs but not truly bilaterally synchronous. This was considered to represent a diffuse abnormality of non-specific type.

It was decided that the patient had recurrence of primary hyperparathyroidism, presumably from another parathyroid adenoma. Because of the limitation in urinary concentration and the elevation of the blood non-protein nitrogen it was now apparent that renal damage had occurred. Accordingly on February 10, 1955 an exploration of the neck was performed by Dr. Laird. The right lobe of the thyroid gland was completely excised and the whole right side of the neck anterior to the carotid vessels exposed. However no abnormal parathyroid tissue was found. Palpation of the left side of the neck was entirely negative. Accordingly, the exploration was discontinued. Pathological examination of the excised thyroid lobe revealed that attached to it were two parathyroid glands and a nest of parathyroid tissue embedded in the lobe itself. Subsequent microscopic examination revealed these to be composed of entirely normal parathyroid tissue.

Postoperatively there was no fall in her serum calcium and because of its subsequent rise to dangerously high levels it was decided to increase the amount of fluids given per day and add potassium supplements to her regimen. On February 11, the administration of duracton ACTH, 0.5 cc. intramuscularly daily, and cortisone acetate, 200 mg. daily, were added to her treatment. The program of hydration and steroids failed to lower her serum calcium and accordingly it was decided to explore the mediastinum. On February 16, during the operation performed by Dr. Laird, the patient's sternum was split, the left side of the trachea was bared and the thymus gland resected. However no parathyroid tissue was found. The evening following operation the patient's condition deteriorated; she became dyspneic and began to cough. Expiratory rhonchi were heard throughout both lung fields. Her apex rate rose to 140, the temperature rose to 102°F. and the blood pressure began to fall. She was placed in an oxygen tent, given digoxin intravenously, sedation and finally norepinephrine intravenously. All this was to no avail and the patient died on the morning of February 18. An electrocardiogram taken just prior to death showed much electrical artifact. However the rate was 180, the rhythm regular and its appearance generally conformed to that of the previous tracing. (Fig. 5.)

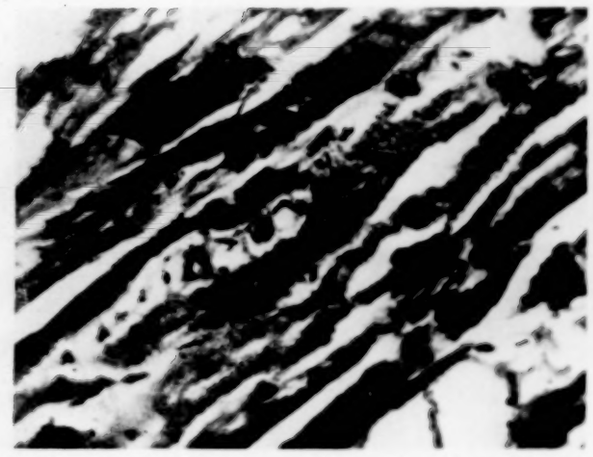

FIG. 6. An area of necrosis in the myocardium. There is loss of nuclei and of normal histological architecture. This change was not accompanied by thrombosis in the capillaries. Calcium could not be demonstrated in these necrotic fibres. Phosphotungstic acid iron hematoxylin stain, original magnification × 360.

A complete autopsy was performed three hours after death. Apart from the two recent surgical incisions, no abnormalities were noted on external examination. The entire neck and mediastinal structures were dissected carefully but failed to show any evidence of tumor. Only a moderate degree of calcification was noted in the scar tissue at the site of the first neck exploration in 1953.

The cardiovascular system showed slight atheromatous change involving the aorta and coronary arteries. On gross inspection the heart was within normal limits but microscopic examination revealed numerous small, diffusely scattered areas of necrosis of muscle fibers with complete loss of normal architecture. (Fig. 6.) This change was not associated with inflammatory cell infiltration, thrombosis of blood vessels or calcium deposition.

The left and right lungs weighed 600 and 745 gm., respectively, and showed acute massive pulmonary oedema. In addition, several small, slightly greyish white nodules could be seen on the pleural surface as well as in the lung parenchyma. (Fig. 7.) These nodules ranged from a few mm. to 1 cm. in diameter and the cut surface revealed minute areas of yellowish discoloration indicating necrosis. Microscopic examination of the metastatic tumor (Fig. 8) revealed only a slight increase in cellular pleomorphism as compared with the original tumor. (Fig. 4.) In the metastasis, however, the predominant cell was the so-called transitional water-clear cell. Very few mitotic figures were seen; one of these is shown in Figure 8. Within the metastases, microscopic areas of necrosis were seen associated with thrombosis of capillaries and calcium deposits.

Examination of the gastrointestinal tract revealed no lesions. The kidneys showed marked bilateral

FIG. 7. Cut surface of the left lung. Note several round tumor nodules in the parenchyma. The largest measured 1 cm. in diameter.

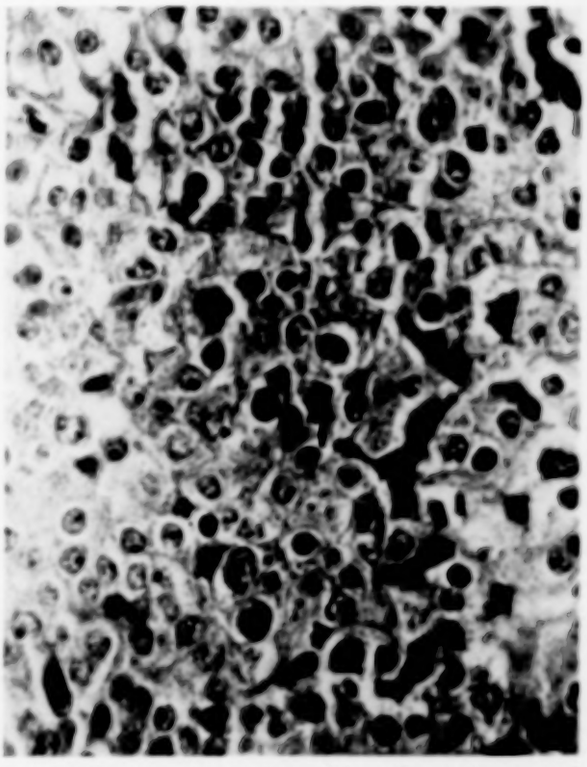

FIG. 8. Metastasis in the lung. The cells are larger and show more pleomorphism than those of the original tumor. Note the mitotic figure in the centre. Hematoxylin and eosin stain, original magnification × 360.

nephrocalcinosis, with nephrolithiasis of the right kidney. The calcium deposition was somewhat streaky in gross appearance and involved mostly the medulla of the kidneys. Larger areas of calcification were surrounded by loose connective tissue and chronic inflammatory cell infiltration. Apart from thrombosis of branches of the uterine veins, no abnormalities were noted in the pelvic organs. The adrenal glands contained small cortical adenomas and the

FIG. 9. Area of osteitis fibrosa cystica in the left fibula.

pancreas showed a slight degree of hyperplasia of the islet cell tissue. The liver showed slight fatty metamorphosis and several branches of the portal vein contained small fragments of emboli, the source of which could not be determined. Examination of the central nervous system, including the pituitary gland, failed to reveal any lesions. The skeletal system showed thinning of the bony trabeculae and the characteristic lesions of osteitis fibrosa cystica in the left fibula (Fig. 9) and pelvic bones. There was some hyaline change in the arterioles of the spleen but no calcification.

COMMENTS

Although the parathyroid tumor was originally considered to be an adenoma, it is obvious from the autopsy findings that it must now be regarded as a carcinoma. There was no indication of this diagnosis before death as the pulmonary metastases were not evident on the chest roentgenogram. The histological appearance of the original tumor, with its preponderance of uniform chief cells, was indistinguishable from that of the adenomas reported in the literature. This similarity of appearance between adenoma and carcinoma of the parathyroid gland has been noted previously [*2,3,5,16*]. However, on careful histological re-examination of the original tumor in our patient a very few mitotic figures were found. It is the contention of Castleman [*18*] that all tumors of the parathyroid gland showing mitotic figures are carcinomas, no matter how infrequent the mitoses. While the subsequent course and autopsy findings of our patient may support Castleman's thesis it is of interest that opposition to this viewpoint has been expressed by Black [*19*] who states that mitotic figures may be found in the tumors of patients whose clinical course is benign. Furthermore it is apparent that in some cases of parathyroid carcinoma no mitotic figures can be found histologically [*1,20,21*].

With the possible exception, then, of mitotic figures, the usual histological criteria of cancer elsewhere in the body do not suffice for the diagnosis of carcinoma of the parathyroid gland. An unequivocal diagnosis of carcinoma can be made only if metastases are found. However, most workers in this field believe that a parathyroid tumor which is densely adherent or locally invasive is a carcinoma [*2,5*]. It is of interest that the tumor in the present case showed no local invasiveness.

While non-functioning carcinomas of the parathyroid glands doubtless occur, it would be extremely difficult to differentiate these from carcinomas arising in the thyroid gland. Hence most authors do not make the diagnosis of parathyroid carcinoma in the absence of evidence of endocrine hyperactivity.

It is noteworthy that no evidence of parathyroid tissue was found in the neck or mediastinum either at operation or at postmortem examination. One must therefore conclude that the seeds of the pulmonary metastases in this case were sown prior to removal of the original tumor in the neck. In view of the normal biochemical findings on the patient's second and third admissions, the metastases could not have been hormonally active at these times. The interval of twenty-two months between operation and the final hospital admission indicates the slow growth of carcinoma of the parathyroid. This feature is emphasized by Black [*5*] who found that the course of the disease in those who have died varied from 8 to 240 months, with an average of 69.5 months.

Our patient showed the most marked electrocardiographic changes of any case of hyper-

parathyroidism that we have been able to find in the literature. Lepeschkin [*22*] states that infusion of calcium chloride in animals or intravenous injection of calcium gluconate in man produces marked vagal bradycardia and depression of T waves. The P-R interval becomes prolonged when large doses are used. The T waves tend to show depression in leads II and III but these are slight. He states also that the hypercalcemia of generalized osteitis fibrosa cystica always results in shortening of the relative Q-T interval, sometimes accompanied by an increase in the P-R interval and inversion of the T waves in leads II and III. Furthermore the P wave characteristically shows a peculiar rounding which may be seen in other causes of hypercalcemia. Ballin in 1932 [*23*] described a patient with an R-T interval of 0.22 seconds preoperatively which changed to 0.26 seconds postoperatively. No other details were given. Kellogg and Kerr [*24*] described a patient, aged seventeen, with a slightly prolonged P-R interval of 0.23 seconds, a shortened Q-T interval of 0.30 seconds and an abnormally low T wave in lead II. Postoperatively there was improvement in these findings. Bradlow and Segel [*25*] described a case of parathyroid adenoma in a fifty-seven year old man whose serum calcium reached 21 mg. per cent. The Q-T_c interval was 0.34 seconds and the S-T segments were almost absent. However there were no negative T waves in this patient's electrocardiogram. A repeat tracing taken five days postoperatively was practically normal. It is difficult to be certain whether the uniformly negative T waves (with the exception of those in lead I) in our patient reflect the hypercalcemia or her diffuse myocardial injury. We suspect the latter alternative.

Our failure to lower the serum calcium with the administration of large doses of ACTH and cortisone is of interest in view of the recent reports in this regard. Dent [*26*] states that with steroid therapy he was able to lower the hypercalcemia of vitamin D poisoning, sarcoidosis and idiopathic hypercalcemia of infancy but failed to achieve this effect in six cases of hyperparathyroidism. Connor et al. [*27*] were able to lower the elevated serum calcium level with the administration of steroids in sarcoidosis, vitamin D intoxication and milk-alkali syndrome. In some patients with hypercalcemia due to malignancies a slower fall occurred and in some no fall at all. Three patients with hyperparathyroidism experienced no decline in serum calcium level with the use of steroids.

Terminally our patient exhibited some of the characteristics of the syndrome known as "parathyroid poisoning" [*28*]. These included nausea, vomiting, lethargy, a rising serum phosphorus and azotemia (minimal in this case). The cause of death in "parathyroid poisoning" is far from clear. In our patient there was no reason to assume a renal cause of death as there was never any oliguria, there were no significant urinary abnormalities and there was no evidence of marked azotemia. Shelling et al. [*29*] administered an overdose of parathyroid extract to dogs and concluded that death in the animals was due to excessive loss of water and electrolytes in the urine. They were able to prevent the symptoms of overdosage by supplying these constituents. However our patient was given large amounts of fluid and balanced electrolytes in an attempt to counteract the effects of hypercalcemia, with no subsequent improvement. It is our conviction that the cause of death in this patient was cardiac in nature. This is evidenced by the marked electrocardiographic changes, the diffuse areas of necrosis found in the heart at autopsy, and the terminal pulmonary edema. In regard to the last point, it should be mentioned that examination of the fluid balance sheets revealed no evidence of overhydration of the patient during her terminal illness.

While it is generally agreed that hypercalcemia may produce electrocardiographic changes, it is uncertain whether the areas of necrosis found in the heart, both in experimental parathyroid poisoning [*30,31*] and in some clinical cases of hyperparathyroidism [*32,33*], are due to parathyroid hormone or to the hypercalcemia produced by the hormone. Cantarow et al. [*30*] in their experiments on dogs were of the opinion that the areas of necrosis preceded calcification. They believed, furthermore, that the necrosis could not be explained by vascular occlusion, as the pathological lesions in no way resembled infarcts. The same conclusions were reached in similar experiments in rats by McJunkin et al. [*31*]. The lesions in the heart of our patient bore no resemblance to infarcts and were not associated with calcification. While neither Cantarow et al. [*30*] nor Collip [*34*] were able to cause organ injury in dogs by the use of calcium infusions, McJunkin et al. [*31*] were able to produce lesions in rats using intraperi-

toneal calcium gluconate infusions. However, when Collip [*34*] added acid sodium phosphate to his calcium chloride infusions he was able to reproduce the lesions and clinical picture of parathyroid intoxication in dogs. Thus there may be a species difference in respect to the efficacy with which calcium infusions produce areas of necrosis in animals.

While "parathyroid poisoning" may be cardiac in nature, it does not follow that structural cardiac lesions must always be present. Smith and Cooke [*35*] published a case in which no cardiac lesions were found and in which death was attributed to "parathyroid poisoning" or "chemical death." However, even if one speaks of "chemical death" in these cases rather than death due to structural damage it is still uncertain whether the responsible agent is parathyroid hormone or hypercalcemia. Arguing from analogy is often fallacious and never constitutes proof, but one must be intrigued by the similarity, in certain clinical conditions, of the changes produced by hypercalcemia and by hypokalemia. For example, hypercalcemia and hypokalemia have similar effects on cardiac excitability [*36*]. Furthermore, patients with primary hyperparathyroidism [*28*] or primary hyperaldosteronism with its associated hypokalemia [*37*] may evince profound thirst and polyuria. In both instances these symptoms usually clear soon after operation. Recently it has been shown that prolonged or severe potassium deficiency can produce defective renal concentrating ability both in animals and in man; the evidence for this has been reviewed recently by Conn and Johnson [*38*]. A similar defect has now been demonstrated in experimental hypercalcemia induced by calcium infusions in man [*39,40*]. Furthermore, both in animals in which potassium deficiency has been produced either by the use of low potassium diets or the use of desoxycorticosterone acetate [*41*], and in man in whom death from hypokalemia has resulted from severe sprue [*42,43*] diffuse areas of necrosis have been found in the heart. These appear to be comparable to those seen in our patient, in other cases of hyperparathyroidism [*32,33*], and in experimental parathyroid poisoning [*30,31*]. The "chemical death" of "parathyroid poisoning" may thus represent a functional effect of hypercalcemia on the heart. It has been known for many years that the perfused, isolated heart undergoes systolic arrest when exposed to excess calcium [*36*]. The similarity in symptoms of "parathyroid poisoning" to those of other causes of hypercalcemia such as vitamin D intoxication, sarcoidosis, and the like has led Thomas et al. [*44*] to refer to the syndrome as "hypercalcemic crisis" since hypercalcemia appears to be the common, determining factor.

SUMMARY

The case of a twenty year old woman with parathyroid carcinoma and pulmonary metastases is presented. This is believed to be the ninth case of parathyroid carcinoma with visceral metastases in the literature.

Reference is made to the difficulty in distinguishing carcinoma of the parathyroid gland from adenoma.

It is believed that the patient described died of "parathyroid poisoning" and that death in this state is cardiac in nature.

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Asymptomatic Pulmonary Alveolar Proteinosis*

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In June 1958 Rosen, Castleman and Liebow [*1*] described a new pulmonary disorder "pulmonary alveolar proteinosis." Since their original description two more cases have appeared in the medical literature,§ one associated with thrombotic thrombocytopenic purpura [*2*], and the other associated with Weber-Christian's syndrome [*3*]. This disease has several diagnostic features, and the purpose of this paper is to report a case incorporating many of these typical findings.

CASE REPORT

This was the first admission to the 1710th USAF Hospital for a thirty-four year old white man, who was admitted for the evaluation of a chest abnormality evident on the roentgenogram taken during a routine periodic physical examination. This man was completely asymptomatic at the time of his admission except for slight soreness in the left side of the chest, which he had noted for three or four days prior to admission. This was described as a dull ache and was unrelated to respiration. The patient had had an occasional mild, non-productive cough, but there was no cough at the time of admission. His weight was stable; there was no history of pleuritic chest pain, productive cough, hemoptysis, dyspnea, night sweats, fever or chills. There was no past history of pneumonia, asthma, whooping cough, tuberculosis, exposure to tuberculosis, use of oily nose drops, aspiration, epileptic seizures or recent unconsciousness. The patient denied ever having worked in a mine or around dust. He had been employed as a transportation supervisor since 1951. From 1946 to 1951 the patient worked in the petroleum section where he had to refuel aircraft and clean gasoline tanks with a pungent solvent. However, he never coughed during this time and noted no respiratory symptoms whatsoever. He never worked about lumber yards and had never been exposed to broken fluorescent tubes. He had used aerosols in the form of "bug bombs" in the past on several occasions.

This man had been in the San Joaquin Valley, California, on three different occasions; once in 1943 for about five months, again in 1948 for seven months, and for a few weeks in 1954. There were, however, no respiratory symptoms at the time. In 1954 an x-ray film of the chest taken during a re-enlistment physical examination showed an abnormality which was described as marked fibrosis in the middle lobe of the right lung and the lower lobe of the left lung, suggestive of bronchiectasis. The patient was, therefore, admitted to an Air Force Hospital in Japan and remained there for a period of four to five days. Apparently, during this time, bronchograms were taken and, although there is no record of the results, the patient states that "everything turned out normal." The diagnosis at that time was as follows: "Admission without disease, suspected bronchitis; laboratory and x-ray data obtained; no disease found." The patient was completely asymptomatic at that time and has been subsequently, except for an occasional non-productive cough. He has had about one to two colds per year and they tend to "settle in the chest." He has noted substernal pain in the chest with colds and has had a cough at these times. The patient had a parakeet as a pet in 1952 and 1953.

This man has fifteen years of military service and has been stationed in Florida (1943), California (San Joaquin Valley, 1943), England and Germany (1943–1946), Virginia (1946–1947), Guam (1948–1949), Texas (1950), Utah (1951), Greenland (1951–1952), Japan (1954–1956), South Carolina (1956–1958).

The patient was born in Virginia; is married and the father of two healthy children. Past history reveals

§ Since this paper was submitted for publication, three additional cases have been reported [*4,5*].

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that the patient smokes a half package of cigarettes per day; he takes aspirin for headaches only occasionally. He had a sinus infection in 1943 while in California, which lasted about five months and was associated with frequent nose bleeds. He was hospitalized in 1954 in an Air Force hospital in Japan for ligation of the long saphenous vein in the right leg because of varicosities. Tonsillectomy and appendectomy was performed during childhood. He had had a laceration of the left leg prior to his entry into the service. He had been unconscious briefly when he was struck while playing football in high school. There was a history of pruritic skin eruption following exposure to wool. He had chicken pox, measles and mumps as a child.

System review was within normal limits. On admission the temperature was 98.0°F.; pulse, 60; blood pressure, 110/70 mm. Hg. The patient appeared to be a well developed, well nourished, cooperative white man in no distress. A complete physical examination was within normal limits except for the lungs. The chest was noted to be symmetrical and the diaphragm moved well. Examination of the lungs showed numerous fine, subcrepitant, high pitched rales, audible in the right axilla, inferiorly. There were a few very coarse rales in the left base, laterally; the breath sounds were coarse in the left axilla and also over the area of the middle lobe of the right lung. There were no abnormalities to vocal or to tactile fremitus.

Examination of the heart showed the rhythm to be regular at the rate of 60 per minute. A_2 equaled P_2. The point of maximal impulse was noted to be 9 cm. lateral to the midsternal line in the fifth left intercostal space. Left border of cardiac dullness was in the same position. There was no murmur, rub, thrill or gallop.

The extremities showed an oval, well healed scar on the anterior aspect of the left leg below the knee, measuring 2 by 7 cm. Peripheral pulses were strong, and there was no clubbing, edema or cyanosis.

Laboratory studies revealed the following: Repeated urinalyses, normal; white count, 8,000/cu. mm.; 63 per cent neutrophils, 35 per cent lymphocytes, 2 per cent monocytes; sedimentation rate, 4 mm. per hour; hemoglobin, 14.9 gm. per cent hematocrit, 44 per cent; C reactive protein, negative. Heterophil agglutinin titers were within normal limits. The serologic test for syphilis was negative; L.E. preparations were negative. The blood urea nitrogen was 11.4 mg. per cent; alkaline phosphatase, 6.4 Bodansky units; cholesterol, 210 mg. per cent, esters, 70 per cent; prothrombin time, 12.5 seconds/control 12.5 seconds; serum sodium, 139 mEq./L.; potassium, 5.3 mEq./L.; chloride, 107 mEq./L.; calcium, 10 mg. per cent; phosphorus, 3 mg. per cent; total serum lipids, 1,089 mg. per cent; glucose tolerance test, normal curve; fasting blood sugar, 81 mg. per cent; serum protein, 6.4 gm., albumin, 4.1; globulin, 2.3 per cent; per cent total serum protein (dye value) albumin, 62, alpha$_{(1)}$ globulin, 4.1; alpha$_{(2)}$ globulin, 4.4, beta globulin, 13; gamma globulin, 16.5; sputum culture: gamma streptococci; gastric washings on three occasions for acid fast were negative on culture and guinea pig innoculation; throat culture: alpha streptococci; complement fixation tests for psittacosis-lymphogranuloma venereum were negative at 1:10 dilution; sputum culture for fungi: no growth; complement fixation test for histoplasmosis: whole yeast phase antigen, negative; histoplasmin, negative; bleeding time, 8 minutes; clotting time, 3 minutes, 30 seconds.

Pulmonary function studies performed by Lt. Colonel Frank L. Miller of the Walter Reed Institute of Research were as follows: Tidal volume, 1,108 cc.; minute volume, 19,958 cc.; respiratory rate, 18 minute; expiratory reserve, 1,068 cc.; inspiratory capacity, 2,715 cc.; vital capacity 3,649 and 3,783 cc.; per cent of predicted normal, 88 per cent; predicted normal, 4,276 cc.; residual volume, 2,897 cc.; total lung volume, 6,680 cc.; air trapped in twelve seconds. none; maximum breathing capacity, 153 L./minute; per cent of predicted normal, 110 per cent; predicted normal, 139 L./minute; residual volume/total lung volume, 43 per cent; expiratory reserve/vital capacity, 28 per cent; timed vitalometry: one second, 7.3 (89 per cent), two seconds, 8.2 (100 per cent), total 8.2; per cent arterial oxygen saturation (room air): one minute sitting, 98.2; exercise, 97.5, recovery, 98.6; two minutes exercise, 97; five minutes supine, 98; seven minutes supine, 98; nine minutes supine, 98; N_2 washout with 100 per cent oxygen (maximum expiration): thirty seconds, 9.5; one minute, 2.5; two minutes, 0; two minutes and twenty seconds, 0; three minutes, 0. Skin tests for histoplasmin, coccidioidin, blastomycin and PPD 1 and 2 were negative.

Roentgenograms of the chest showed the appearance of a soft infiltrate radiating from the hilar areas and confined primarily to the medial one-third of each lung field. (Figs. 1, 2 and 3.) This appearance was more pronounced in the lower lobe of the right lung than in the other regions. There did not seem to be any significant hilar adenopathy.

These findings were considered compatible with those described in pulmonary alveolar proteinosis.

Roentgenograms of the hand showed no significant bone changes. Views of the paranasal sinuses showed some generalized haziness over both maxillary sinus regions; however, no fluid levels were seen. The frontal and ethmoid areas appeared normal. This appearance was compatible with the diagnosis of chronic maxillary sinusitis bilateral.

The electrocardiogram was within normal limits.

The patient was afebrile throughout his entire hospital course. He was cooperative and on August 1, 1958, biopsy of the right scalene node was performed. On microscopic examination the specimen was interpreted as showing reactive hyperplasia. Following

FIG. 1. Photoroentgenogram obtained in January 1951, showing no significant pulmonary or cardiac abnormalities.

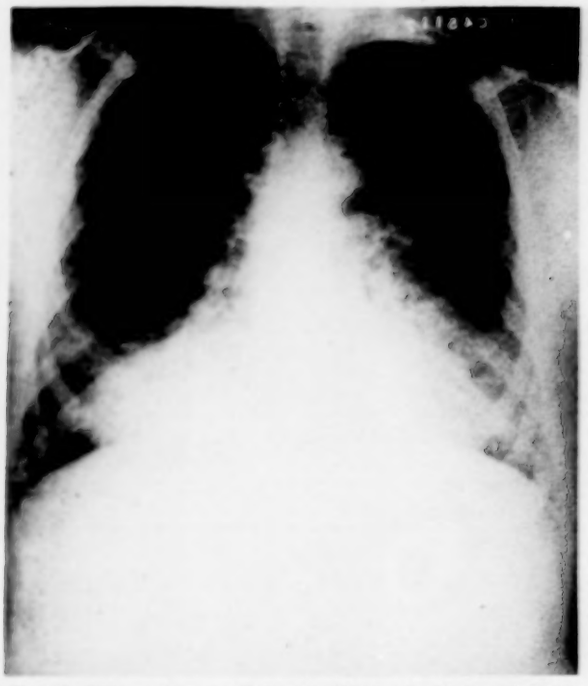

FIG. 2. Film taken on July 18, 1958, showing soft infiltrate radiating from the hilar areas and confined primarily to the medial one-third of each lung field. There is no significant hilar lymphadenopathy.

FIG. 3. Lateral film taken on July 18, 1958, showing diffuse involvement, particularly of the anterior lung field.

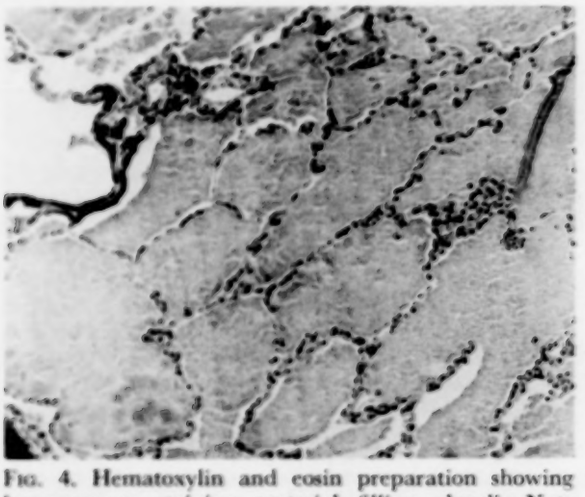

FIG. 4. Hematoxylin and eosin preparation showing homogeneous staining material filling alveoli. Note intact alveolar septums. Bronchiole in upper left with intact mucosa.

this, the patient was transferred to Maxwell Air Force Base Hospital for thoracotomy and biopsy of the lung. He was subsequently transferred to the Walter Reed Army Hospital where he had his third examination. The results were negative. On October 16 a left thorocotomy was performed with resection of the left sixth rib. The surgeon did not note any pleural adhesions. In the apices, posterior and anterior segments of the upper lobe, and the first portion of the lingula, and in the superior segment and diaphragmatic surface of the lower lobe, the lung had a yellowish gray appearance. The lung was also nodular and granular. Biopsy of what appeared to be normal lingula and transition zone to disease, as well as a portion of the anterior segment of the upper lobe

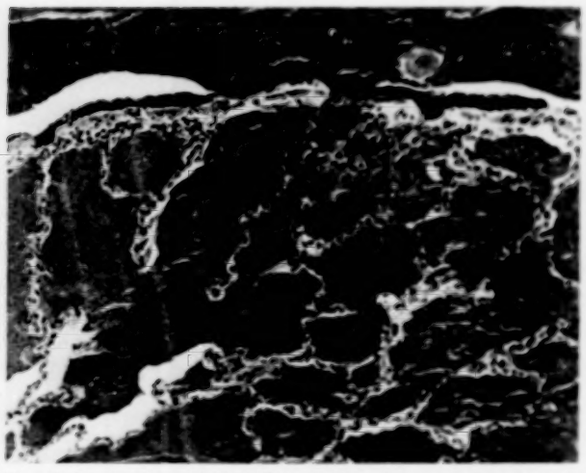

FIG. 5. Periodic acid-Schiff stain showing acicular spaces, intact alveoli and rounded masses representing partially disintegrated cells.

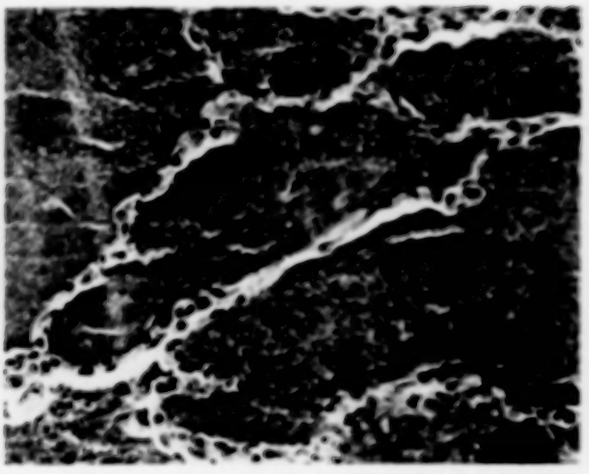

FIG. 6. Higher power periodic acid-Schiff stain of section of Figure 5 showing similar changes.

of the lung where the disease appeared to be most marked, was performed. The pathology report of the specimen by Colonel R. S. Aronson of the Walter Reed Army Hospital and by Dr. S. H. Rosen of the Armed Forces Institute of Pathology was: "Biopsies of lingula and anterior segment of upper lobe left lung, pulmonary alveolar proteinosis." (Figs. 4, 5 and 6.)

Bacteriological studies made by Captain Eugene B. Blair, Walter Reed Institute of Research, predominating organism: Corynebacterium species, cultural and microscopic examination was negative for acid-fast bacilli. Guinea pig inoculation was negative. Attempts to isolate a virus by Captain R. T. Johnson, Walter Reed Institute of Research in monkey kidney, HeLa and fibroblast tissue cultures were unsuccessful.

COMMENTS

Pulmonary alveolar proteinosis is a chronic pulmonary disease of unknown etiology characterized histopathologically by intra-alveolar deposition of a proteinaceous periodic acid-Schiff positive substance, which is high in lipid content. This material, according to Rosen et al. [*1*], represents the end product of a degenerative process involving mononuclear cells ("septal cells") found in the alveolar walls. The probable sequence of events is as follows:

1. Proliferation and enlargement of "septal cells" accompanied by the appearance of periodic acid-Schiff positive granular material in the cytoplasm.
2. Sloughing of cells into the alveolar lumens.
3. Nuclear disintegration and disarrangement of the cytoplasm with resultant aggregates of periodic acid-Schiff positive substance.

The appearance of "laminated bodies," probably an intermediate step in this transformation, represents laminated deposition of periodic acid-Schiff positive substance around incompletely disintegrated "septal cells" [*1*]. (Figs. 4, 5 and 6.)

The clinical picture of this entity is non-specific. Progressive dyspnea and coughing, which was usually productive, were the chief presenting symptoms in Rosen's cases. About half of the patients had febrile illness which at first was considered to be pneumonia. Other non-specific complaints were also noted including chest pain, fatiguability and slight loss of weight. Physical findings were remarkable by their absence. Only four of the patients in the original group had rales. Three showed clubbing, and one was found to have impaired resonance. The clue to the diagnosis may be found in the x-ray picture. (Figs. 2 and 3.) Radiographically "there is a fine, diffuse, perihilar, radiating, feathery or vaguely nodular, soft density, resembling in its butterfly distribution the pattern seen in severe pulmonary edema." The key to this radiological picture is the absence of clinical findings which would suggest pulmonary edema. Sarcoidosis, with which this radiological picture could be confused, can be distinguished by the absence of hilar adenopathy [*1*].

The present case is unusual in certain respects. This patient, in contradistinction to the others described, was and is totally asymptomatic. He has no dyspnea, cough or other symptoms. If an x-ray of the chest was not required as part of a routine physical examination, his disease,

for the present, would not have been detected. It is unfortunate that the roentgenograms taken in Japan in 1954, which showed "Marked fibrosis in the right middle lobe and in the left lower lobe," are not available. However, it is likely that the "fibrosis" observed at that time was in reality proteinosis. Since then, he has been on full active duty and has had no complaints. The earliest chest roentgenogram available, taken in 1951, is a perfectly normal one. As in the other cases described, a clue to the etiology of this disease is not apparent. The fact that, since the publication of the original paper, one case is described associated with Weber-Christian disease [3] and another with thrombotic thrombocytopenic purpura [2] suggests that this disease is probably not due to one common etiologic agent. No real pattern of common exposure to a chemical inhalant is apparent. Roentgenograms taken of all Base personnel exposed to petroleum and involved in refueling or cleaning petroleum tanks did not reveal any other persons with an abnormality of the chest. Chest roentgenograms of all the members of this patient's family were within normal limits.

SUMMARY

A case of pulmonary alveolar proteinosis is described, and corroborative data including representative radiographs and photomicrographs of the biopsy specimen of the lung are presented.

The majority of patients discussed in the original monograph by Rosen et al. were symptomatic. The case presented here offers a unique opportunity to follow the natural history of this condition and to observe the effects of various therapeutic programs on its course.

Acknowledgment: We gratefully acknowledge the kindness of the Walter Reed Army Hospital and Drs. John T. Elkins, Jr., Frank L. Miller and Helmuth Sprinz of that institution in making available the pathologic material in this case.

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Pulmonary Alveolar Proteinosis*

A Correlation of Pathological and Physiological Findings in a Patient Followed Up with Serial Biopsies of the Lung

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An apparently new pulmonary disease entity has been described by Rosen, Castleman and Liebow [*1*]. The criteria for the disease, pulmonary alveolar proteinosis, were established on histological grounds. One of our patients was briefly included in the first published series of this new disease. A further follow-up of over thirty-two months in this patient, with multiple biopsies of the lung performed and serial studies of pulmonary function, may be of value to other observers as more cases of pulmonary alveolar proteinosis are uncovered. The disturbances in physiological function have been correlated with the previously described alterations in histology.

The clinical course has been variable in the cases of this disease initially described. Our patient was a previously healthy young white man who had noted gradually increasing exertional dyspnea with progression to marked dyspnea at rest, fatigue, anorexia, marked weight loss and finally cyanosis. At this point a remitting type temperature curve developed in the patient with evening temperatures of 101°F and he was admitted to a sanatorium for treatment of suspected tuberculosis. Vigorous search for tubercle bacilli failed to uncover any organisms and the patient was referred to Jefferson Hospital for further study and treatment. The picture was somewhat complicated by a history of exposure to silica dust for a two and a half month period some four to five months prior to the onset of his symptoms. Studies which will be cited shortly would appear to rule out silicosis as a specific etiologic factor.

METHODS

The vital capacity, maximum breathing capacity, and timed vital capacity were measured with a 13.5 L. Collins respirometer. The index of intrapulmonary mixing and functional residual capacity was measured in duplicate by the open circuit oxygen inhalation method of Baldwin, Cournand and Richards [*2*]. The expired air was collected in a 125 L. Tissot gasometer. Expired gases were analyzed for O_2 and CO_2 by the micro-Scholander technic [*3*]. Duplicates were required to check within .03 per cent. Arterial blood was obtained through an indwelling Cournand needle placed in the brachial artery and analyzed for oxygen content, oxygen capacity, and CO_2 content using the Van Slyke and Neill manometric apparatus [*4*]. Duplicates were required to check within .022 ml. per 100 ml. for oxygen and within .4 ml. per 100 ml. for CO_2 [*5*]. Carbon dioxide tensions were calculated from the line charts of Van Slyke and Sendroy, and the Henderson-Hasselbalch equation. Arterial oxygen tensions were measured directly by the bubble equilibration technic of Riley, Proemmel, and Franke [*6*] using 50 mm. capillaries with a 0.5 bore fused to tuberculin syringes. Equilibrations were carried out in a constant temperature water bath maintained at 37 ± 0.2°c. Duplicate determinations were required to check within 5 mm. Hg. Arterial pH was measured at 37°c. with a Cambridge electron-ray research model pH meter. Alveolar oxygen tensions were calculated on the basis of the alveolar gas equation. The physiological dead space was calculated from the Bohr formula, substituting arterial blood pCO_2 for alveolar pCO_2. Analysis of ventilation-perfusion relationships and of the diffusion characteristics of the lungs was made according to the methods devised by Lilienthal, Riley et al. [*7*], and extended by Riley, Cournand and others [*8–10*].

CASE REPORT

A detailed presentation of the case history follows:

I. W., a twenty-five year old white male garbage collector, was first admitted to the Barton Memorial Division of Jefferson Hospital in March 1956 because of progressive respiratory distress. The patient dated the onset of his symptoms to four months prior to

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FIG. 1A. Roentgenogram of chest (February 1956). Biopsy specimen taken from right upper lobe of the lung at this time.

FIG. 1B. Roentgenogram of chest (March 1957). Biopsy specimen taken from left lower lobe of the lung at this time.

admission when he first noted gradually increasing dyspnea on exercise. This was accompanied by ease of fatiguability, weakness, anorexia, and a forty pound weight loss. A non-productive cough was present unaccompanied by hemoptysis. Cyanosis was initially observed one month later. One month prior to his first admission he was hospitalized at a tuberculosis sanatorium because of the severe dyspnea. At this time the clinical course was complicated by the development of fever and chills. X-ray films showed a disseminated infiltration of both lung fields involving all but the apices and basal costophrenic areas. (Figs. 1A and B.) Skin tests for tubercle bacilli and histoplasmosis were negative as were sputum studies for tubercle bacilli and fungi. Polycythemia was evident at this time. Treatment with oxygen inhalation and bronchodilators provided only temporary relief. The patient was then transferred to the Barton Memorial Division of Jefferson Medical College Hospital for further study and treatment.

The past medical and family history was non-contributory. Occupational history revealed that prior to his work as a trash and garbage truck driver the patient had worked for a pulverizing company. Here silica sand was pulverized into silica flour, which the patient would then load into sandbags. A mask was worn to protect against the excessive dust. The patient retained this position for two and a half months during the summer of 1955. His occupational history was otherwise unrevealing and there was no known exposure to broken fluorescent light bulbs during his job as trash and garbage collector.

Physical examination had revealed a well developed, acutely ill, cyanotic, dyspneic young white man showing evidence of recent weight loss. The patient was normotensive and respirations were 26 per minute. There was a plethoric facies with cyanosis of the lips, mucous membranes and ears. Dental hygiene was extremely poor. The chest was symmetrical with good equal expansion. There were no rales or rhonchi on auscultation and only minimal bilateral diminution of breath sounds. Examination of the heart showed no abnormalities except for the tachycardia of 108 and an accentuated P_2. There was no hepatosplenomegaly or lymphadenopathy. There was definite clubbing of the fingers and toes accompanied by cyanosis of the nail beds. The remainder of the examination was within normal limits.

Results of laboratory studies were within normal limits except for a hemoglobin of 17.9 gm. per 100 ml. The electrocardiogram showed evidence of a vertical axis with clockwise rotation. The venous pressure was 110 mm. of H_2O with an arm-to-tongue circulation time of nineteen seconds (Decholin®). Physiological evaluation of pulmonary status was performed after which a biopsy specimen of the right upper lobe of the lung was obtained. (See Section "Methods"). At this time the patient's arterial oxygen saturation at rest was only 66.6 per cent with a significant decrease on exercise. The spirographic pattern was one of marked restriction without evidence of an obstructive component. These findings were thought to be consistent with the diagnosis of alveolar-capillary block syndrome. The histological interpretation of the biopsy material was descriptive rather than definitive and the exact nature of the disease remained in question. Cultures of the tissue for tubercle bacilli and various fungi were negative. The patient was treated with penicillin, tetracycline, streptomycin, and intermittent positive pressure breathing without

FIG. 1C. Roentgenogram of chest (September 1958). Biopsy specimen taken from right lower lobe of the lung at this time.

any apparent clinical effect. During this time the fever abated without any apparent direct correlation with the treatment used. Frequent breathing of 100 per cent oxygen was necessary for symptomatic relief. Because of the extent of the lesion and the marked functional impairment the prognosis was considered to be extremely guarded. Administration of Meticorten,® 10 mg. three times a day, was instituted and the patient was discharged to return in one month for further evaluation. On readmission in April 1956 the patient felt some mild subjective improvement, but results of physical examination and laboratory studies including x-rays of the chest were essentially unchanged. Administration of Meticorten was decreased to 10 mg. twice a day.

Examination on readmission in May 1956 revealed that the patient's clinical picture had changed little. Dyspnea and marked cyanosis were still present. During this admission the patient was bronchoscoped. Apart from a moderate quantity of tenacious mucopurulent secretions and the friable, dusky colored mucosa, the examination was negative for abnormalities. A study of secretions for bacteria, fungi, acid-fast bacilli and cancer cells revealed no abnormalities. A protein electrophoretogram showed a mild elevation of the alpha$_2$- and beta-globulin components. Because of the lack of apparent improvement on steroids, Meticorten was discontinued. At the same time administration of saturated potassium iodide solution was begun.

On readmission in September 1956 for further physiological studies the patient was much better symptomatically. The results of physical examination and x-ray films were essentially unchanged since the previous admission. Arterial blood was now 87.9 per cent saturated at rest, which represented a marked improvement since April 1956. There was also definite improvement in the vital capacity.

Because of continued symptomatic improvement the patient was desirous of returning to light work. The roentgenographic appearance (Fig. 1B) had not essentially changed since the onset of the illness, although there had been evidence of physiological improvement. Accordingly a second biopsy specimen was obtained from the left lower lobe of the lung in March 1957. The pleural cavity was free and the lung appeared orange-tan and was studded diffusely subpleurally with nodules 2 mm. to 4 mm. in size. The biopsy specimen was found to be almost identical histologically with the specimen taken one year previously and the diagnosis was still in doubt. Results of laboratory studies were normal except for a hematocrit of 57 per cent, and hemoglobin of 17.6 gm. per 100 ml. The saturated solution of potassium iodide had been maintained during this period and the patient was again discharged on this treatment.

The patient returned for his seventh admission in November 1957. There had been further gradual improvement during the intervening period and he had been able to return to his job as a garbage truck driver. His only complaint was dyspnea on moderate exertion. The roentgenographic appearance was essentially unchanged. The hemoglobin was 16 gm. per 100 ml. with a hematocrit of 53 per cent and a white blood cell count of 5,250 per cu. mm. with a normal differential. Pulmonary function studies again showed significant improvement with arterial oxygen saturation now being 91.2 per cent at rest and dropping to 84.3 per cent on exercise.

On his eighth admission in June 1958 the patient was completely asymptomatic except for mild dyspnea on marked exertion and he had returned to his normal pattern of living. There was no cyanosis present and the digital clubbing had completely disappeared. The physical examination was within normal limits, except for the bilateral small thoracotomy scars. Hemoglobin was now 13.9 gm. per 100 ml. and the hematocrit was 39 per cent. The x-ray of the chest for the first time revealed a definite partial clearing of the diffuse pulmonary lesions. Results of physiological studies showed further return to normal values and the arterial oxygen saturation at rest was within normal limits.

In September 1958 the patient was readmitted for another biopsy of the lung. He was entirely asymptomatic. The x-ray of the chest showed marked further clearing. (Fig. 1C.) A biopsy specimen was obtained from the right lower lobe of the lung and the patient was discharged.

COMMENTS

The diagnosis of pulmonary alveolar proteinosis in this case is based on its histological charac-

FIG. 2A. Biopsy specimen of the lung (March 1956). Granular proteinaceous material in alveolar spaces. Original magnification × 100.

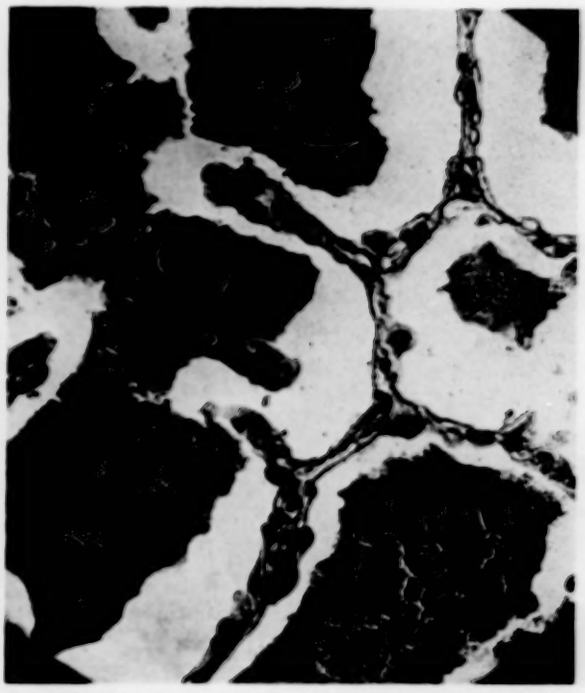

FIG. 2B. Biopsy specimen of the lung (March 1956) Granular proteinaceous material and enlargement of alveolar lining cells are quite apparent. Original magnification × 400.

teristics. The inclusion of this case in the original series of Rosen, Castleman and Liebow [*1*] attests to its fulfilling their representative criteria. (Figs. 2A and B.) The histological features accordingly have been well described by these authors. The representative deposition of a PAS-positive granular and floccular proteinaceous material within the lumens of distal air spaces was present. There were also minimal changes in the interalveolar septa although in certain small areas some interstitial fibrosis was noted on the second biopsy specimen. (Fig. 3.) This specimen taken one year after the initial biopsy otherwise revealed the same histological characteristics as the first specimen. Despite the period of steroid therapy in the interim and the moderate improvement in the patient's clinical course, there were no appreciable differences between biopsy specimens. At no point was there evidence of silicosis.

As the original authors had noted, the ultimate fate of the lesions is difficult to predict on the basis of the material now available. In one case they noted interstitial fibrosis was present in a biopsy specimen of the lung taken four years after the presumed onset of the disease, and it could not be stated whether this was a response

FIG. 3. Biopsy specimen of the lung (March 1957). Granular proteinaceous material in alveolar spaces. Original magnification × 100.

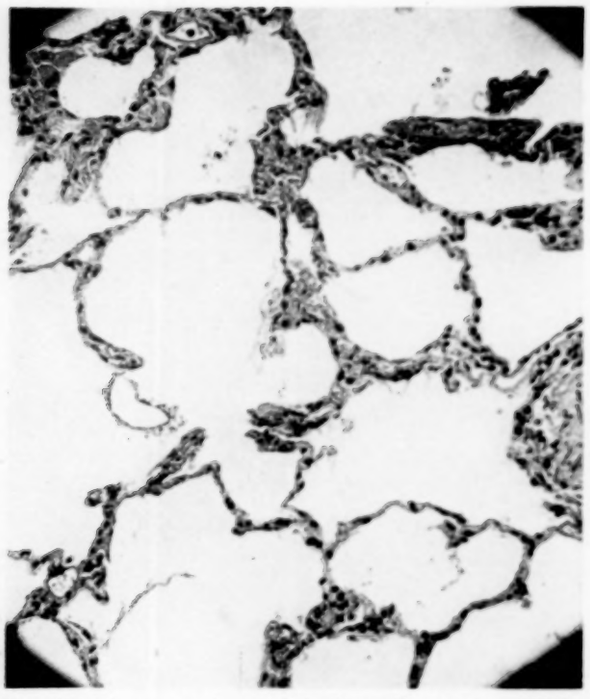

FIG. 4A. Biopsy specimen of the lung (September 1958). Marked clearing of alveoli with focal thickening of some alveolar walls. Original magnification × 100.

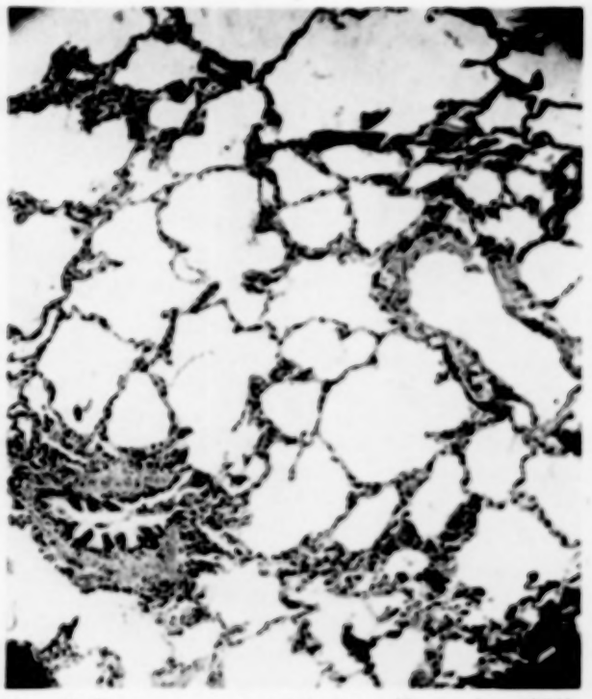

FIG. 4B. Biopsy specimen of the lung (September 1958). A small amount of proteinaceous material persists and some of the alveolar lining cells retain their granularity. Original magnification × 400.

to the disease or a concomitant finding. It was also mentioned that radiographic changes compatible with interstitial fibrosis occurred during the course of the disease, constituting shaky evidence that interstitial fibrosis might be an end result. Because of the desire for information as to the natural evolution of the disease as well as its ultimate prognosis, a third biopsy specimen of the lung was obtained when our patient was markedly improved and asymptomatic. The x-ray film showed that the lung had almost completely cleared and the physiological picture had returned close to normal limits.

The biopsy specimen was taken in a area of the right lower lobe, which had apparently cleared, but was thought to have been previously involved, on the basis of the x-ray films. The specimen grossly appeared normal. On microscopic examination there had been marked to almost complete clearing of the proteinaceous material originally observed in the alveolar spaces. (Figs. 4A and B.) Indeed, evidence of one or two small nests of this acidophilic material could be found only on careful observations in contrast to the almost total involvement in the two previous surgical specimens. There was some slight to moderate thickening of the alveolar septa and a very slight increase of connective tissue in patchy areas. It was thought to be questionable that these minor changes could be attributed to previous involvement with proteinosis as they represented changes in type and scope otherwise often seen. In several small areas, however, there were some alveolar cells showing the same granular characteristics observed in the more classic biopsy specimens. (Figs. 4A and B.) This is believed to represent an early stage in the development of the proteinaceous material. Histologically it would be impossible to say whether these represented possible areas of recrudescence or merely areas of incomplete regression. This may correlate with the clinical tendency to remission and re-exacerbation with progression observed in some cases. In addition it should be mentioned that in none of the biopsy specimens was there any real evidence of vascular change.

The history of an occupational exposure to silica, even though this exposure was of short duration, was of great concern in the original investigation of this case. This was obviously more true then, as the disease entity into which this case falls had yet to be described. The silica sand to which the patient had been exposed was

shown on analysis by several different investigators to be essentially quartz (98 per cent) with traces of ferromagnesium mineral and feldspar. SiO_2, 98 per cent; alumina, 1 per cent; titanium, .05 per cent; and Fe_2O_3, .05 per cent. In size the particulate range was 15 per cent less than 1 μ; 61 per cent less than 3 μ; 81 per cent less than 5 μ; and 95 per cent less than ten μ. Petrographically the particulate matter trapped in the alveolar exudate and in the alveolar walls appeared to be dominantly carbonate and no quartz particles were visable in the size range 2 to 3 μ or greater.

The x-ray diffraction analysis of the lung tissue for silica revealed: ash per cent of dried lung tissue, 5.9 per cent; total SiO_2 per cent of ash, 0.08 per cent; free SiO_2 per cent of ash, 0.7 per cent; mineral identified quartz, 0.7 per cent. The quantity of ash was believed to fall in the range for normal subjects with no industrial exposure. The total silica content was on the low side of the range for normal subjects but the quantity of free silica as quartz was beyond the range of values for normal subjects, although less than the range for persons who had anatomical silicosis [*11*].

The histological picture and the various tissue and material analyses appeared to have ruled out silicosis as the cause for the pulmonary pathology. The possibility that this might have represented an early "acute silicosis" once entertained has been discarded in the light of the clinical course with its marked symptomatic and anatomic improvement. If this were an early stage of acute silicosis, progressive fibrosis and continued disability would have been expected rather than the clearing that has occurred.

The possibility that the disease in this patient represents a non-specific reaction to a readily identifiable irritant dust remains an interesting conjecture. This would be in accord with the belief of the original workers that the disease may represent a tissue response to a variety of non-specific chemical irritants. It is interesting that one of our consultants, Dr. Dutra [*12*], in the earlier attempts to define the clinical picture, noted that he had seen a somewhat similar appearance in experimental work in animals. This was noted in the lungs of animals that had been breathing inert dusts of extremely fine particulate matter in large concentrations within the lung. There was a response of the septal cells similar to that observed in the specimens from our patient. An eosinophilic protein material as well as the dust was found in the acini and there was a slight interstitial fibrosis. In view of this, it is interesting to speculate whether continued exposure to an irritant, such as silica flour, in this case, would result in repeated or prolonged attacks of the disease or in eventual interstitial fibrosis.

That this disease, as now recognized, is a far from benign process can be seen by the eight deaths reported in the original twenty-seven cases. Pulmonary insufficiency as manifested by progressive dyspnea and cyanosis occurred terminally in at least five cases. In addition exertional dyspnea sufficient to cause invalidism in several cases still persists and this has apparently been an integral factor in almost all the cases. We believe that the extensive pulmonary function studies performed on our patient during two and a half years of observation, together with some of the data collected by the original authors affords us an insight into the mechanisms of the pulmonary insufficiency. The initial determinations were performed at the apparent nadir of his illness.

PULMONARY FUNCTION

It can be seen that there has been a marked and steady improvement in all the affected parameters of pulmonary function studied since the original studies in March 1956. (Tables I and II.) This has parallelled the clinical improvement, as would be expected, and has indeed preceded the roentgenographic evidences of improvement.

The spirograms at the initial study showed a marked decrease in vital capacity to 2,221 cc. (47 per cent of predicted) with a comparatively excellent preservation of maximum breathing capacity of 113 L. per minute (86 per cent of predicted normal). In addition there was a marked reduction of total lung capacity to 3,340 cc. with a preservation of a normal residual volume to total lung capacity ratio of 27 per cent. The patient was hyperventilating at rest (9.6 L per minute per M^2) and despite this was able to maintain an arterial oxygen saturation of only 66.6 per cent. The arterial oxygen saturation after exercise fell to 51 per cent. These findings are typical of the alveolar-capillary block syndrome. The administration of 50 per cent oxygen increased the arterial oxygen to 85.2 per cent and 100 per cent oxygen in the inspired air increased the arterial oxygen to only 98 per cent.

TABLE I

PULMONARY FUNCTION STUDIES

Date	Arterial Oxygen Saturation							Arterial Oxygen Tension (mm. Hg)						Alveolar-Arterial Oxygen Gradient (High) (mm. Hg)			Alveolar-Arterial Oxygen Gradient (Low) (mm. Hg)			Calculated pCO_2 (mm. Hg)	pH	Physiological Dead Space		Tidal Volume (cc.)	Diffusing Capacity of the Lung for Oxygen cc./min. Hg	Venous Admixture (%)
	Rest (%)	Exercise (%)	With Different Concentrations of Inspired Oxygen (%)					With Different Concentrations of Inspired Oxygen (%)														cc.	Tidal Volume (%)			
			14	16	30	50	100	20	14	16	30	50	100	P_AO_2	PaO_2	Gradient	P_AO_2	PaO_2	Gradient							
3/12/56	66.6	51	....	....	..	85.2	98	34	..	..	45	62	107	162	45	117	106	34	92	35	7.39	310	52	549		
4/11/56	87.9	....	79.9	....	..	....	..	59	..	45	..	..	...	95	59	36	65	45	20	46	7.34	272	55	492	12	31
3/4/57	87.6	77.5	81.6	....	..	....	..	57	..	47	..	..	...	95	57	38	73	42	26	44	7.38	....	59	....	12	28
11/8/57	91.2	84.3	....	....	..	....	..	..	..	..	..	..	...	....	....	....	....	....	....	48	7.32	257	55	471	....	....
6/9/58	96.3	90.0	92.2	92.8	..	....	..	85	78	..	..	..	...	90	85	5	68	67	1	41	7.38	239	45	526	25	2

TABLE II

PULMONARY FUNCTION STUDIES

Date	Inspiratory Capacity (cc.)	Expiratory Reserve Volume (cc.)	Total Lung Capacity (cc.)	Residual Volume (cc.)	Residual Vol./Total Lung Capacity X 100 (%)	Vital Capacity (cc.)	Vital Capacity Predicted (%)	Three Second Vital Capacity (%)	Maximum Breathing Capacity		Compliance	Index of Intrapulmonary Mixing	Minute Ventilation (L./min./M²)	Oxygen Removed in Ventilation (cc./L.)
									L./Min.	Predicted (%)				
3/12/56	1730	705	3340	905	27	2221	47	100	113	86	....	1.20	9.57 (16.8)	21.0
9/11/56	1763	1269	....	....	..	2989	63	100	122	94	....	....	6.89 (12.06)	26.8
3/14/57	....	1563	....	....	..	3169	67	100	125	93	96 cc./cm. H_2O	....	5.8 (9.8)	33.0
11/8/57	....	....	....	....	..	3123	66	100	129	96	....	....	6.2 (11.3)	29.3
6/9/58	2301	1580	5729	1648	31	3681	82	98	121	91	105 cc./cm. H_2O	1.19	5.0 (9.2)	33.8

The inability to fully saturate the arterial blood with the administration of 50 per cent and 100 per cent oxygen was noted and although not a component of the alveolar-capillary block syndrome can be adequately explained on the basis of the histological changes present. The extent of the physiological impairment at that time was so marked it was felt that death would occur shortly.

Physiological studies six months later, however, showed a definite improvement, correlating well with his symptomatic improvement. The vital capacity was then 2,989 cc. (or 63 per cent of predicted normal) with a maximum breathing capacity of 122 L. per minute (94 per cent of predicted normal), and the arterial oxygen saturation was 87.9 per cent at rest. Further improvement has occurred subsequently so that now the vital capacity is 3,881 cc. (91 per cent of predicted normal); 98 per cent three second vital capacity; maximum breathing capacity of 122 L. per minute (91 per cent of predicted normal); total lung capacity of 5,729 cc.; and resting ventilation of 5.0 L. per minute per M^2. In addition the patient exhibits normal arterial oxygen saturation at rest of 96.3 per cent with only a mild fall to 90.0 per cent on exercise.

There are many features present in this data and apparently in some of the data observed in other patients which suggests this is an example of the alveolar-capillary block syndrome. This syndrome has been previously described in berylliosis, sarcoidosis, chronic interstitial pneumonitis, scleroderma of the lung, acute miliary tuberculosis [*14*], histocytosis of the lung [*15,16*], asbestosis [*17*], eosinophilic pneumonia [*18*], and postirradiation fibrosis [*19*]. Some of the characteristic features which were present in our patient were the marked reduction in lung volumes with normal residual volume to total lung capacity ratio, well preserved maximum breathing capacity, hyperventilation at rest, and apparently normal distribution of inspired gases as indicated by the alvolar N_2 content of 1.20 per cent following the inhalation of 100 per cent oxygen for seven minutes. In addition there was anoxemia at rest with marked increase in anoxemia following exercise. This was accompanied by normal arterial carbon dioxide tensions. Partial confirmation of these findings appears in the data presented by Rosen et al. where there was a reduction in vital capacity with a preservation of maximum breathing capacity in several cases. In two cases arterial oxygen saturations were below 50 per cent terminally. In two other cases the alveolar-arterial oxygen tension gradient was found to be 20 mm. Hg and 89 mm. Hg, although this latter figure represented gradients obtained during exercise rather than at rest.

Direct determination of the arterial oxygen tensions were done for confirmation and for estimation of the degree of block present. These revealed marked alveolar-arterial oxygen tension gradients with a high gradient of 117 mm. Hg with the patient breathing 30 per cent oxygen. Subsequent determinations of gradients revealed improvement which corresponded to the improvement observed clinically and in the other physiological parameters. One year after the initial gradients, the observed alveolar-arterial oxygen tension gradient at rest on room air was markedly decreased, although still significantly elevated at 35 mm. Hg. Calculation of the diffusing capacity of the lung for oxygen showed values of from 5 to 12 cc. of oxygen per mm. Hg pressure difference, per minute, all of which were lower than normal.

The presence of an alveolar-capillary block syndrome as the cause for the pulmonary insufficiency in one patient, and probably in other cases of pulmonary alveolar proteinosis, would thus appear to be established. That this may be one of several causes rather than the sole cause may be inferred from several pathological and physiological observations. Morphologically alveolar-capillary block has usually been accompanied by some process involving the alveolar septum either inflammatory, granulomatous, or neoplastic in nature [*20*]. As was noted in the original descriptions of alveolar proteinosis the relative lack of cellular infiltration in the interalveolar septa has been characteristic. The alveolar-capillary block may have been produced by the partial occlusion of the alveolus and impingement of the diffusing surface by the proteinaceous material similar to the effect of edema fluid in acute pulmonary edema. In addition there has been noted a transformation of the "septal cells" in the wall of the alveolus with increase in number and size which may represent the actual precursors of the proteinaceous material. It is quite possible that this alteration both in size and number and possibly also in biophysical properties of the cells may present an increased impediment to the diffusion of oxygen.

Certain features suggest that increased venous admixture or physiological shunting may also

play a role in the production of anoxemia. The marked anoxemia at rest (originally 66.6 per cent), while consistent with alveolar-capillary block, is greater than usually seen when there is no superimposed infection. The ability to raise the arterial oxygen to only 85.2 per cent on the administration of 50 per cent oxygen and inability to fully saturate the patient with 100 per cent oxygen would suggest physiological and/or anatomical shunting. These concentrations of oxygen in the inspired air should almost always result in full saturation of the arterial blood where alveolar-capillary block is the sole cause for the anoxemia. In addition it has been suggested that the administration of a low oxygen mixture will generally result in an increased tension gradient when the problem is primarily one of diffusion. The lower oxygen mixture minimizes the effect of venous admixture on the calculated gradient. Our studies would seem to indicate a mixture of both these mechanisms in our patient. In several instances administration of a gas with a lesser oxygen tension resulted in a decreased gradient. In September 1956, for example, the gradient was 36 mm. Hg on room air and decreased to 20 mm. Hg when the patient breathed a 16 per cent air-oxygen mixture. This would indicate that part of the increase in tension gradients was due to higher than normal venous admixture. The still significant elevation of the gradients both at room air and on the low oxygen mixture is attributed to the presence of the alveolar capillary block.

Review of the histology reveals how readily this physiological shunting could occur. In large sections of the tissue observed, large groups of alveoli were filled with proteinaceous material with little alteration in the adjacent blood vessels. Thus groups of alveoli which could probably not be ventilated at all were being perfused in an approximately normal fashion. Blood leaving this area would retain the same characteristics as regards oxygen and CO_2 content as upon entry and in essence would represent venous blood. This would then be reflected in the peripheral arterial blood as anoxemia.

The pathophysiology would then appear to be a result primarily of alveoli being either completely or partially filled by the granular and floccular proteinaceous material characteristic of the disease. Complete filling in large areas results in increased venous admixture and physiological shunting. Less complete filling of the alveolus results in impairment in diffusion of the alveolar-capillary block type to which alteration in the biophysical properties of the septal cells themselves may play an additive role. The improvement of the lungs volumes with the clearing of the disease indicates that the restrictive pattern was due to occupation of potentially air-occupying space by the proteinaceous material and confirms that there is little fibrosis. Lung compliance measured during the course of the disease was significantly decreased as would be expected, with marked alveolar filling. The apparent lack of significant improvement of lung compliance at a time when there was marked improvement roentgenologically, clinically and physiologically remains difficult to explain. The lack of significant changes in the electrocardiogram during the course of the disease is also somewhat difficult to explain. Part of this may be attributed to the lack of changes in the pulmonary vasculature. In many other instances of alveolar-capillary block the interalveolar changes have resulted in impingement or disruption of the capillary bed. Effects on the vascular bed have not been marked in pulmonary alveolar proteinosis, histologically, and this may explain why the changing course of the disease has had relatively no influence on the electrocardiograms.

Treatment of the disease at present is symptomatic, involving the use of oxygen as needed; expectorants and antibiotics for superimposed infection. The administration of adrenal steroids for a short time in our patient, as in the other cases cited by Rosen, did not appear to be accompanied by any improvement. However, there did not appear to be any rebound phenomena associated with its withdrawal as has been noted in treatment of the Hamman-Rich syndrome. The role of iodides and vitamin therapy in the improvement of our patients' condition must, of course, remain a matter for conjecture. Iodides may have caused a softening of the alveolar proteinaceous material allowing it to be more readily absorbed or expectorated. The pulmonary insufficiency and the loss of pulmonary reserve in these patients is apparent at most times. When, in addition, there is superimposed respiratory tract infection, even of minor extent, their condition is seriously effected and death may ensue. This phenomenon has been observed in other instances of marked pulmonary insufficiency as in obstructive emphysema, Hamman-Rich syndrome, silicosis and sarcoidosis. General supportive and symptomatic

measures may be of great importance at those times and may help the patient survive until natural remission occurs.

The prognosis in our patient must remain somewhat guarded due to the present lack of knowledge of the natural course of the disease. The marked clinical, histological and physiological improvement over a thirty-two-month period is most encouraging. The fact that remissions have occurred in other patients, however, without ultimate clearing must temper our enthusiasm somewhat. Further studies in this patient and other patients over a period of time will be necessary before a more definitive appraisal of ultimate prognosis can be advanced.

SUMMARY

A case of pulmonary alveolar proteinosis followed up with serial biopsies of the lung performed over a two and a half year period is presented. Extensive pulmonary function studies during that period are included, with a correlation of the pathological and physiological findings.

The patient at the peak of his illness exhibited marked pulmonary insufficiency due both to alveolar-capillary block and increased venous admixture.

The pathological, physiological and roentgenographic findings have shown a marked improvement over a two and a half year period. This has been accompanied by progressive improvement in his clinical status to the point that he is now symptom-free. The ultimate prognosis must remain guarded, however, because of the obscure etiology of the disease and our present lack of knowledge as to its course.

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Hypoglycemia Associated with Pancreatic Islet Cell Tumors*

Review of the Literature and Case Report of a Malignant Tumor

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SINCE Nicholl's initial report [*1*] in 1902 of a pancreatic islet cell tumor, a total of some 600 of these neoplasms has been described in the world literature. At the time of Howard's article [*2*] in 1950, 398 cases could be collected, the remainder having appeared in the eight intervening years. By far the large majority of these tumors, usually estimated at about 90 per cent, are non-malignant and of the simple islet-cell adenoma type. The remaining 10 per cent includes neoplasms of a malignant nature. Howard's comprehensive review included thirty-seven such malignancies, of which twenty-two had been proved malignant on the basis of metastasis and also exhibited unequivocal signs of excess insulin production with repeated hypoglycemic episodes. To the present time, to my knowledge, seventeen additional cases of metastatically proved malignancies exhibiting hyperinsulinism have been recorded [*3–18*], the case in the present communication representing the fortieth such tumor described since Wilder's initial report in 1927 [*19*].

It is not only the relative rarity of these types of tumors which makes them so interesting, but also the associated syndromes of hyperinsulinism and hypoglycemia. Since Harris in 1924 [*20*], two years after Banting and Best discovered insulin, proposed the theory of hyperinsulinism, this symptom complex has become more and more readily recognized and the causes thereof better understood. Nevertheless, patients suffering from hypoglycemic attacks are still often misdiagnosed [*6,17*] and frequently regarded as epileptics, psychotic, hysterical, or cases of brain tumor. This usually contrasts tragically with the fact that a correct diagnosis, institution of simple drug therapy and diet, with or without surgery as indicated, could provide an effective, lasting and often life-saving cure. We believe it worthwhile to review the subject of hypoglycemia, using the following case as an interesting example.

CASE REPORT

A fifty-six-year old white, married, male railway freightyard worker was admitted to the hospital in August 1956 with a chief complaint of periodic dizziness of twenty-five to thirty years' duration. The patient gave a very clear and graphic account of having had almost daily episodes of dizziness, tingling sensations of the extremities and circumoral region, and stumbling while walking. Associated with these symptoms there was also profuse sweating. Occasionally a glassy stare of the eyes had been noticed by his fellow employees. The onset of these attacks was usually about 3:00 P.M., but also in late morning. The patient claimed that such attacks could always be relieved by eating something such as a candy bar. There was also a history of irritability and confusion occurring between meals for many years, always disappearing after intake of food.

His referring physician (Dr. D. D. Durgin of Newport, Vermont) revealed that when first seen by him the patient had been semicomatose, confused, and irritable when stimulated. He had continued in this state for about two hours with outbursts of very aggressive activity. A blood sugar determination showed a value of 40 mg. per cent. The response to intravenous administration of glucose was dramatic, the patient becoming perfectly rational and cooperative almost immediately; he was amnesic for the previous four hours, however. A high protein, high fat, low carbohydrate diet was instituted, but this did not control the symptoms, and the patient was unable to work. An exploratory laparotomy was performed at another hospital, at which time the pancreas was found to be of normal size, consistency and shape. The

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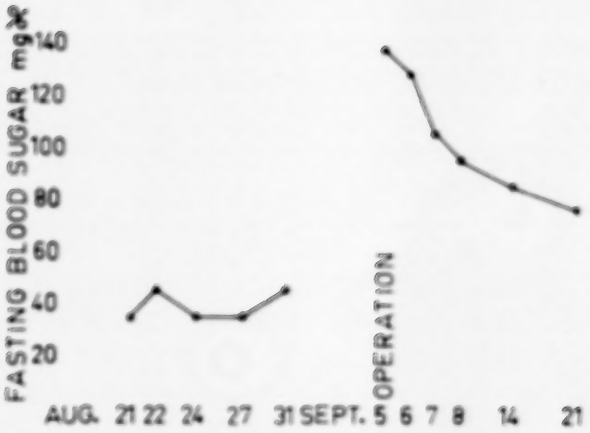

FIG. 1. Fasting blood sugar levels in reported case. Preoperative fasting levels are consistently below 45 mg. per cent. The level rose to 137 mg. per cent one hour postoperatively and then dropped progressively to normal levels during the ensuing two weeks.

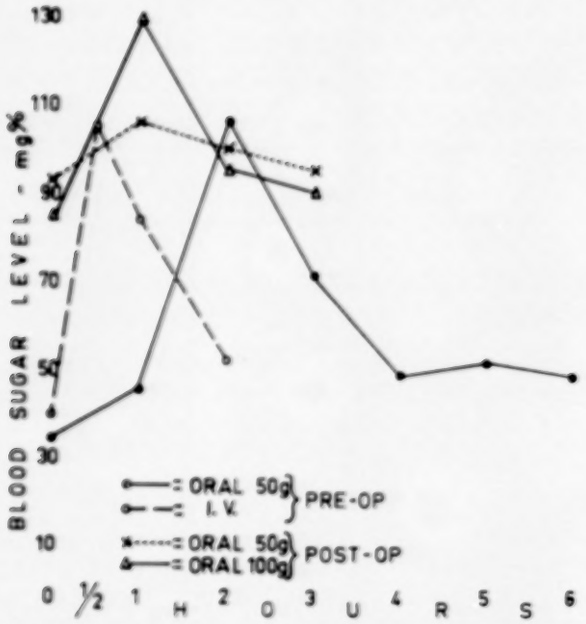

FIG. 2. Glucose tolerance tests in reported case. Delayed response in preoperative oral test but fairly normal intravenous reponse. Postoperative oral tests (both within ten days after surgery) revealed progressive return toward normal handling of a glucose load.

entire organ was carefully inspected and palpated but no abnormalities were noted. No aberrant pancreatic tissue was seen. It was not thought advisable to perform any further surgical procedure. Following recovery from this operation the patient returned home and adhered to his low carbohydrate diet without improvement. Attacks of hypoglycemia seemed to increase in both frequency and severity

The past history, the family history and the patient's personal history revealed nothing pertinent. His daily work in the freightyards involved heavy physical activity with lifting of large weights.

Physical examination on admission to our hospital showed normal vital signs. The patient was a well developed, well nourished middle-aged man. The results of the entire examination, including neurological review, were within normal limits.

Laboratory data received from the other hospital showed: red blood cell count, hemoglobin and white blood cell count to be within normal limits with a differential of 40 per cent polymorphonuclears, 10 per cent stab forms and 49 per cent lymphocytes. Urinalysis was within normal limits; bromsulfalein retention in forty-five minutes, 6.7 per cent; and a total eosinophil count of 110/cu. mm. A glucose tolerance test was carried out but the results were regarded as unreliable because of suspected errors in the test solutions.

Laboratory determinations after admission to our hospital showed much the same differential white blood cell count and blood and urine tests were within normal limits. Bromsulfalein retention was 2.2 per cent in forty-five minutes; serum bilirubin 0.3 mg. per cent; serum total protein 6.1 with albumin/globulin of 3.3/2.8 gm. per cent; thymol turbidity 4 Ducci units; cephalin flocculation test 1 plus at twenty-four and forty-eight hours; serum sodium 141 mEq./L.; serum potassium 4.9 mEq./L.; serum chloride 106 mEq./L. A twenty-four-hour urine collection contained 145 and 36 mEq./L. of sodium and potassium respectively. A forty-eight-hour stool collection revealed dry feces weight to be 91 gm. with a fatty acid content of 27.5 gm. or 30 per cent of the dry weight. The basal metabolic rate was plus 21 per cent (on a poor tracing). The fasting blood sugars and glucose tolerance tests are summarized in Figures 1 and 2. An epinephrine sensitivity test showed a fasting blood sugar level of 32 mg. per cent. A half hour after administration of 0.3 ml. of 1:1000 solution epinephrine the fasting blood sugar level had risen to 61 mg. per cent and remained at 66 mg. per cent at the one-hour determination.

X-ray films of the heart and lungs showed no abnormalities. An upper gastrointestinal series showed no abnormalities of the esophagus, stomach or duodenal cap. The small bowel pattern was noted to be grossly abnormal, with loss of the fine, feathery appearance of the jejunum and coarsening of the jejunal folds. There was marked spasticity of the small bowel with puddling of the barium. It was suggested that these changes alone might be expected to give abnormal results in any test depending on intestinal absorption such as the oral glucose tolerance test. These jejunal changes were noticeably increased in a repeat examination one week later.

Evaluation of the patient following these examinations strongly suggested that there was an organic basis for his hypoglycemia, despite the previously unsuccessful laparotomy. The hepatic function

appeared normal. The significance of the roentgenographic findings was not easily evaluated. A constant, maintained state of hyperinsulinism appeared to be present, and the patient was therefore referred to the surgical service for re-exploration and eventual partial pancreatectomy in the event that no isolated pancreatic lesion could be found.

Two weeks following admission to the hospital the patient was prepared for surgery with 500 cc. of a 10 per cent glucose solution and the abdomen was re-explored by Dr. A. G. Mackay. The operative findings included a large opening in the transverse mesocolon through which most of the small bowel had herniated. In the neck of the pancreas approximately anterior to the superior mesenteric artery and vein, a nodule of approximately 1.5 cm. in diameter was found near the upper surface of the organ. This was bluish in appearance and had lying above it two dark-colored areas which were grossly characteristic of lymph nodes. The gross appearance of the tumor was rather characteristic of an islet cell tumor. There was poor encapsulation, but the surrounding area of the pancreas appeared grossly normal, as did the posterior surface of the head of the pancreas, the liver and gallbladder. With the patient under continual spinal anesthesia a resection of the pancreatic mass and three adjoining lymph nodes together with a biopsy of the liver was performed.

Microscopic examination of the tumor showed the usual morphology of islet cell tumor. Of the three lymph nodes which were also excised one showed areas of islet cell morphology mixed with normal lymph node tissue. In both the primary tumor and the lymph nodes there was no appreciably atypical appearance of the cellular nuclei. However, the node in which clusters of islet cell tumor were found was clearly physically distinct from the pancreatic tumor, and it was the pathologist's opinion that this represented a discrete metastasis to the peripancreatic lymph nodes. Biopsy specimen of the liver showed no abnormalities.

The patient's postoperative course was uneventful and both symptomatically and from laboratory findings he showed a rapid return to normal. One week postoperatively a repeat gastrointestinal series showed definite improvement in the small bowel pattern.

The patient has been followed up for twenty-two months since operation. During that period his weight has returned to normal and his appetite has been good. There have been no further symptoms of hypoglycemia, and the results of a fasting blood sugar test performed in May 1958 showed a normal level of 85 mg. per cent.

Hypoglycemia—Its Causes and Symptoms. The syndrome of hypoglycemia is usually divided into the two main etiologic categories of organic and functional. The latter form of so-called spontaneous hypoglycemia, i.e., occurring without exogenous administration of insulin, is even today a poorly understood phenomenon. Organic hypoglycemia, on the other hand, implies a definitely demonstrable anatomic basis for the phenomenon of spontaneously lowered blood sugar, and it is, of course, to this group that the islet cell tumors belong. The 1947 classification of Conn [*22*] given in Table 1 helps to clarify the various possible etiologies.

Whatever the actual cause involved, an abnormally lowered blood sugar is the feature common to all types of hypoglycemia and is responsible for a series of symptoms which is almost pathognomonic of the condition. Wauchope in 1933 [*23*] defined the various stages of progressive hypoglycemia, and his observations are as valid now as twenty-five years ago. As in our case, the patient first experienced a strange weakness and perhaps lightheadedness. This is followed by the second stage, of "adrenalin secretion," the body's attempt to maintain homeostasis through liberation of liver glycogen stores, characterized by sweating, palpitation, hunger and anxiety. If the patient is not given or does not himself take some form of carbohydrate at this point, he then progresses to inarticulate speech, incoordination, bizarre and often combative behaviour, and finally convulsions and coma. It is to be strongly emphasized that whereas simple therapy in the form of intravenous glucose during the early stages will effect a total remission of symptoms within a few minutes, patients in the later stages of cerebral depression may not respond no matter how much glucose is administered [*17*]. Although the patient may regain consciousness, irreversible central nervous system changes may have occurred from the prolonged hypoglycemia and coma. As pointed out by Webster [*24*], hypoglycemic coma may paradoxically be accompanied by a normal blood sugar level, and the physician may thus easily be misled if he relies entirely on this laboratory finding. Intravenous glucose will, in such a case, provide a much less dangerous course of action than reliance on the laboratory findings and further waiting.

Certain variations in the mode of appearance of hypoglycemic symptoms are frequently seen. Differences in the rate of fall and in the degree of fall of the blood sugar level undoubtedly influence the rate of appearance and severity of symptoms. In general, a sharp fall over a short period of time will produce more marked

TABLE 1
ETIOLOGIC CLASSIFICATION OF SPONTANEOUS HYPOGLYCEMIA*

I. Organic—recognizable organic lesion
  A. Hyperinsulinism
    1. Pancreatic island cell adenoma
      a. Single
      b. Multiple
      c. Aberrant
    2. Pancreatic island cell carcinoma
      a. Localized
      b. With metastases
    3. Generalized hypertrophy and hyperplasia of the islands of Langerhans
  B. Hepatic disease
    1. Ascending infectious cholangiolitis
    2. Toxic hepatitis
    3. Diffuse carcinomatosis
    4. Fatty degeneration or "fatty metamorphosis"
    5. Glycogenosis (von Gierke's disease)
  C. Pituitary hypofunction (anterior lobe)
    1. Destructive lesions (chromophobe tumors, cysts)
    2. Atrophy and degeneration (Simmonds' disease)
    3. Thyroid hypofunction (? secondary to pituitary hypofunction)
  D. Adrenal hypofunction (cortex)
    1. Idiopathic cortical atrophy
    2. Destructive infectious granulomas
    3. Destructive neoplasms
  E. Central nervous system lesions (hypothalamus or brain stem; interference with nervous control of blood sugar)
II. Functional—no recognized anatomic lesion but explainable on basis of unusual somatic function
  A. Hyperinsulinism (imbalance of the autonomic nervous system): hypoglycemic fatigue; nervous hypoglycemia; functional hypoglycemia; reactive hypoglycemia
  B. Alimentary hyperinsulinism (rapid intestinal absorption)
    1. After gastroenterostomy
    2. After gastric resection (partial or total)
  C. Renal glycosuria (severe degrees of low renal threshold for dextrose)
  D. Lactation
  E. Severe continuous muscular work
III. Miscellaneous
  A. Factitious (surreptitious insulin administration)
  B. Postoperative hypoglycemia
  C. Severe inanition
  D. Unknown

* CONN, J. W. The diagnosis and management of spontaneous hypoglycemia. *J. A. M. A.*, 134: 130, 1947.

and severe symptoms than a gradual decline. It has often been observed that a rapidly falling blood sugar level will cause more pronounced symptomatology at higher blood levels than a slowly declining level. Such a rapid disruption of glucose homeostasis does, in effect, not allow the body to accommodate adequately, and this has been explained on the basis of a rapidly falling blood sugar level producing a greater tissue differential in glucose concentration [*22*].

The etiological basis for the hypoglycemia will also affect the appearance of symptoms. Generally, a functional or idiopathic hypoglycemia is characterized by the onset of symptoms a few hours after eating, whereas the hypoglycemia secondary to the hyperinsulinism of islet cell tumors has no such relationship to food, but is classically brought out through prolonged fasting. Irregular and capricious discharge of insulin from these tumors often produces no regular pattern of appearance of symptoms, and remission from symptoms for periods of months or even years are described [*25*]. Our patient showed an unusual regularity with regard to the time of day he became dizzy or weak. In such a case a more or less relatively constant discharge of insulin from the tumor must be postulated. In general, malignant islet cell tumors have a shorter history of symptomatology, "almost invariably under two years" [*6*], although this did not pertain to the case presented here or to several others in the literature. On the other hand, the hypoglycemic episodes associated with malignant tumors often initially appear only a few weeks before the patient succumbs to his disease [*6,8*]. With regard to malignant tumors with long-standing histories, it is possible that an originally benign tumor has undergone malignant degeneration. Shaw [*11*] suggests "dysfunction of the adrenosympathetic-anterior pituitary mechanism" resulting in islet cell proliferation, cell imbalance and transition from an adenoma to carcinoma.

Insulinomas—Types, Diagnosis and Treatment. Hyperinsulinism as a cause of hypoglycemia is a property of the functioning insulinomas. These neoplasms, both benign and malignant, present interesting subjects for study although difficulties in their identification and classification have arisen. According to Feldman et al. [*9*] six distinct types of tumor can be distinguished, depending not only on the histological picture but on their clinical manifestations as well. Benign tumors can be divided into (1) those associated with hypoglycemia (the "functioning" variety), (2) those without hypoglycemia (or the non-functioning), and (3) those present in diabetic patients exhibiting hyperglycemia. Reports of all types are to be found, in addition

to which in eight recorded cases [*26*] the adenomas have been multiple and scattered throughout the pancreas. In identifying a benign adenoma Warren's criteria [*27*] are quite reliable in that (1) the morphological arrangement of the tumor cells resembles that of normal islets, (2) there is a definite capsule about the tumor, (3) adjacent tissue shows evidence of compression, and (4) the tumor is usually at least 1 cm. in diameter. Although it is difficult to explain why one tumor is of the functioning type and another not, the histological identification of benign adenomas usually presents no great difficulties.

Contrary to this, however, the problem of what constitutes a malignant islet cell tumor has long been discussed in the literature. It would seem best for several reasons to designate as malignant only those tumors with proved metastases. Histologically a truly benign tumor may exhibit extremely atypical cellular morphology. On the other hand, a tumor which is in fact malignant may offer no hint of this histologically. We therefore subscribe to Feldman's classification of the malignant tumors into (1) those with hypoglycemia, (2) those without hypoglycemia [*28–31*], and (3) a group of histologically malignant but clinically benign tumors. In this latter group we would favor placing those reports in the literature in which the diagnosis of malignancy rested solely on histological examination of the primary tumor without demonstrable metastases and in many of which long cures are reported [*24,32–34*].

By 1950, twenty-two tumors of the functioning variety which were definitely malignant had been reported. Listed as suspicious on the basis of microscopic morphology were an additional forty-eight neoplasms, both with and without hypoglycemia. Since that time seventeen other functioning malignancies have been described and at least eight functioning tumors believed to be malignant but without proved metastases [*36–38*]. One case is reported [*18*] in which the primary tumor was thought to be non-functioning, but the hepatic metastases were the site of increased insulin production.

So-called "islet cell hyperplasia" has been mentioned as a type of organic change responsible for hyperinsulinism, but serious doubts have been raised as to whether this is a real entity or merely a normal, unequal distribution of islet cells in various portions of the pancreas. Skillern and Rynearson [*35*] and Porter and Frantz [*40*] report no "hyperplasia" seen in large groups of cases of spontaneous hypoglycemia.

Hypoglycemia associated with tumors demonstrating a fibroma- or sarcoma-like structure and not necessarily connected anatomically with the pancreas have been described in recent years [*39,40*]. With one exception, these tumors do not suggest atypical islet cell neoplasms. An excellent discussion of the various histological types of functioning tumors was recently given by Porter and Frantz [*40*].

For the diagnosis of insulinomas a high index of suspicion remains one of the most valuable assets. Should the suspected patient respond to intravenous glucose it then remains to establish whether the disturbance be functional or organic in nature, and if organic whether or not on the basis of an islet cell tumor. In this instance Whipple's classic triad of criteria [*41*] can often be of help. According to this, an islet cell tumor is (1) always associated with a fasting blood sugar level below 50 mg. per cent, (2) characterized by symptoms which appear after fasting, and (3) is relieved by the administration of glucose. Suggestions have been made to add a fourth and fifth criteria to this list as diagnostic aids. Howard [*2*] advises a trial low carbohydrate diet, lack of response to which would weigh against a diagnosis of functional hypoglycemia. Kornfeld [*42*] suggests a fifth finding of abnormal electroencephalographic tracings during attacks, and he outlines typical disturbances in these recordings.

Unfortunately, the glucose tolerance test, whether performed orally or intravenously, does not give constant and reliable information in distinguishing islet cell tumors from other organic causes of hypoglycemia [*39,43*], although differentiation from the glucose tolerance curve of functional hypoglycemia is usually relatively simple. In the latter condition the "typical" tolerance curve will show a normal fasting level, quick rise to hyperglycemic levels following administration of glucose, and then at two to six hours a drop to markedly hypoglycemic levels, usually followed by a gradual return to normal levels again. Conn [*44*] proposes a standard preparatory diet prior to performing the glucose tolerance test, but even this precaution does not insure a curve characteristic of hyperinsulinism. Long [*45*] suggests that the result of the glucose tolerance test for hyperinsulinism will show a low fasting level, a peak of less than 120 mg. per cent, a return to subnormal levels in

less than two hours and maintenance of this level for five to six hours when the patient has been prepared with an adequate carbohydrate diet. However, both low flat curves and diabetic curves have been seen, and their interpretation is frequently more confusing than helpful. Other complicating factors with reference to the glucose tolerance test include variability of glucose absorption depending on the amount given orally [*15*], and unpredictable abnormalities such as that evidenced by our patient's x-ray film of the small bowel.

Long also suggests that the diagnosis of hyperinsulinism is supported if an infusion of 1 gm./kg./hour of glucose over a period of two hours does not result in hypoglycemia and glycosuria. The epinephrine sensitivity test, helpful in ruling out a hepatic deficiency of glycogen stores, also cannot be relied on too heavily in a differential diagnosis. Various other laboratory tests such as the levulose tolerance test of hepatic function have been put forward but remain inconstant aids. Repeated low fasting blood sugar levels thus remain one of the cornerstones in the diagnosis of hyperinsulinism.

The age and sex of the patient is of little if any aid in differentiation of the various causes for hypoglycemia, the different forms appearing at all ages. In children and infants, however, the diagnosis is often considerably more difficult to establish than in adults because of unusually low blood sugar levels, frequent lack of symptoms, and rapid appearance of symptoms following short fasts [*43,43*]. However, as with most other malignant neoplasms, the malignant insulinomas tend to favor the middle-age groups. The physical examination is usually unrewarding in establishing a diagnosis. The tumors are much too small for palpation in the vast majority of cases. Patients with benign insulinomas, however, may often be noted to be quite obese owing to frequent ingestion of glucose to ward off their hypoglycemic symptoms. The other forms of organic hypoglycemia are, on the contrary, more often associated with a weight loss. This latter sign can also be helpful in guessing the benign or malignant nature of an already diagnosed tumor. An additional observation of perhaps some small aid is the frequent occurrence of obviously neurotic tendencies in patients with purely functional hypoglycemia. The relationship of the psychic to the physiologic aberration is imperfectly understood, as is the fact that the latter often recedes completely during psychotherapy. From the history one may obtain a clue as to whether or not a suspected tumor may be malignant, as it is reported [*11*] that such neoplasms are often the cause of epigastric pain radiating to the left costal margin and back. The significance of the duration of symptoms has already been mentioned. Radiographic examinations in the form of splenoportography have been of use in the hands of Siguier et al. [*12*], and Kelly [*47*] has utilized urinary insulin assays to aid diagnosis.

In the final analysis then, formulation of the diagnosis of a functioning islet cell tumor is largely a process of exclusion of other causes for hypoglycemia. This process is based on the history of the occurrence of the hypoglycemic attacks, their relation to food intake, the less reliable results of physical examination, and laboratory and therapeutic tests. In attempting to establish or verify a diagnosis of islet cell tumor, diseases of the liver and disorders of the adrenal and pituitary glands are the main causes of hypoglycemia to be excluded. Lastly, a warning should be given concerning those persons who give themselves an injection with insulin, thus producing a variable degree of non-spontaneous, organic hypoglycemia [*48*]. Of those cases published the majority have occurred in nurses. Such malingering will, of course, present even greater difficulties in diagnosis.

Whereas the diagnosis of insulinoma often presents great difficulty, therapy is just as often simpler and completely effective. This therapy is surgical and consists of excision of the tumor or tumors via (1) localized extirpation of a visualized isolated neoplasm or (2) subtotal pancreatectomy when a tumor buried in the pancreas is suspected or when multiple adenomatosis is present. Two-thirds of these growths are found in the body and tail of the pancreas, most of the remainder in the head and only a very small number in the neck [*49*]. The large majority of the malignant tumors have been found in the tail. Characteristically, insulinomas are brown, dark blue or blue-black when they lie on the surface of the pancreas. Those of a malignant nature are often larger than the benign tumors and may show gross lymph node or hepatic metastases, or in some cases local spread [*6*] or hemorrhagic tendencies. These are, of course, often inoperable. As in Benesova's report [*4*], even a primary malignant tumor may not be seen at operation although metastases are evident. The malignant nature of the neo-

plasm may not be confirmed, however, until autopsy many years after removal of what was initially diagnosed as a benign adenoma [3]. The so-called "problem in the operating room" which arises at laparotomy when the pancreas appears normal and no metastases are evident is well discussed elsewhere [40]. If a careful and complete preoperative work-up has been made, subtotal pancreatic resection is advised.

Chemotherapeutically, treatment has been attempted using both ACTH and cortisone with variously reported results [50–52]. For hypoglycemia secondary to benign tumors this therapy, although initially successful, must be regarded as only preparatory to surgery, and indeed it may have no effect at all in these cases as opposed to the success described with its use in the functional type of hypoglycemia. Instances of malignant insulinomas with functioning metastases are certainly worth a trial of such therapy, and a good result has been obtained with ACTH in one such case, according to Baumgartner and Reynolds [18], as well as with cortisone in the patient treated by Mason [16]. Alloxan has been used intermittently with poor results for the most part. Conn [53] describes a case of malignant islet cell tumor in which alloxan caused destruction of the normal islets but apparently had no effect on the neoplastic cells. Alloxan is also capable of causing severe damage to the liver without affecting the neoplasm [15].

In contradistinction to the functional type of hypoglycemia, a high carbohydrate diet is indicated in these cases of hyperinsulinism secondary to tumors. As previously mentioned, patients themselves will spontaneously undertake such a diet and carbohydrate consumption at times may reach staggering proportions, several thousand grams daily being ingested.

The prognosis for a single operated islet cell adenoma is excellent. In those instances in which the adenoma is not solitary, as in multiple adenomatosis, or when the tumor is hidden in the pancreas, partial pancreatectomy gives a good chance of cure. Reoperation for reappearance of symptoms appears, however, to be unavoidable in a certain number of cases of the foregoing types, as the possibility of a persisting undetected lesion is always present. The prognosis in proved malignant lesions with demonstrable metastases is poor, as borne out by the literature. However, long term cures in the "microscopically malignant" group of tumors are not unusual.

SUMMARY

A case is presented of long-standing hypoglycemic attacks proved to be caused by an apparently malignant functioning islet cell tumor of the pancreas, with lymph node metastases. To my knowledge this is the fortieth such case to be recorded.

The syndrome of hypoglycemia, and the symptomatology, diagnosis and treatment of hyperinsulinism due to islet cell tumors are discussed.

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Urethane-Induced Hepatic Failure in Man*

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THE use of urethane (ethyl carbamate) as a therapeutic agent in neoplastic diseases, particularly in the leukemias and related disorders, is well established and is based upon the capacity of the drug to arrest mitotic activity [*1*]. It is recognized that this drug has a specific toxic action on the hematopoietic system, producing anemia, leukopenia and thrombocytopenia. A few cases of hepatic damage associated with the use of urethane have been reported. These reports incriminate urethane as the causal agent of hepatic damage, although some authors state that multiple therapeutic modalities were employed in individual cases. In these instances the relation of hepatic damage to the use of urethane may be open to question.

This report reviews all the available reported cases of hepatic damage in human subjects associated with the use of urethane and adds another fatal case which has been studied clinically and pathologically. When these data are considered in the light of the uncommon incidence of this complication of urethane therapy in human subjects, it is suggested that the damage to the liver following the use of urethane in usual dosage schedules is not due to a specific hepatotoxicity but falls into the category of an individual idiosyncrasy appearing during treatment.

CASE REPORT

J. R. (No. 56-A-1239), an eighty year old Negro woman, was admitted to the District of Columbia General Hospital because of fainting spells and hallucinations. The patient gave a history of having had hypertension for fifteen years, and had suffered from fractures of the right humerus and the right hip fourteen and seven months previously, respectively. Examination of blood and bone marrow revealed that she had multiple myeloma. She was treated with transfusions; Serpasil® and urethane were administered, and she was discharged to an outpatient status one month after her admission. She was maintained on urethane therapy, 2 gm. twice a day, for a total of seventy-seven days, until a week before her second admission. During this period the patient had no complaints. On the seventy-seventh day of therapy she complained of anorexia which lasted for the next seven days and during which time she ceased her medication. On the seventh day of the anorectic period she experienced pain and tenderness in the right upper quadrant, and was readmitted to the hospital. Pertinent physical findings were a blood pressure of 210/80 mm. Hg, pulse rate of 96 per minute, and a temperature of 98.6°F. There was slight tenderness in the right upper quadrant and a liver palpable 3 fingerbreadths below the right costal margin. Roentgenograms of the chest revealed a right hydrothorax and osteolytic lesions of the left ribs. Cholecystogram failed to outline the gallbladder due to lack of concentration of the dye. On the sixth day of hospitalization severe jaundice developed which was progressive and was associated with lethargy. The patient died in a coma on the nineteenth day of hospitalization.

During her last admission the pertinent laboratory data were as follows: The urinalysis was negative for Bence Jones protein. A bromsulphalein test showed 62 per cent retention in twenty minutes. Examination of the blood demonstrated an icterus index of 50 units; van den Bergh total bilirubin, 17.6 mg./100 ml., 9.8 mg. of which was direct reacting; alkaline phosphatase 17.3 Bodansky units; thymol turbidity 2.5 units; total proteins 6.1 gm./100 ml., with albumin 2.5 gm., globulin 3.6 gm.; prothrombin time normal; and SGO transaminase 105. The blood urea nitrogen varied from 26 to 34 mg./100 ml. The white blood cell count ranged from 3,350 to 7,000 cells per cu. mm.; neutrophils ranged between 57 and 76 per cent, lymphocytes from 18 to 37 per cent; platelets were 278,000 per cu. mm., hematocrit 37 per cent. The spinal fluid was icteric but otherwise normal.

The patient received supportive therapy including antibiotics, barbiturates and cortisone during this period.

The pathologic findings disclosed that the liver weighed 990 gm. The capsule was smooth, slightly thickened, opacified and congested. The organ was extremely soft. The cut surface revealed a friable, bile-stained parenchyma, punctuated by irregular areas of congestion, hemorrhage and softening. The lobular pattern was indistinct. The hepatic arteries and veins were not occluded. The intrahepatic and

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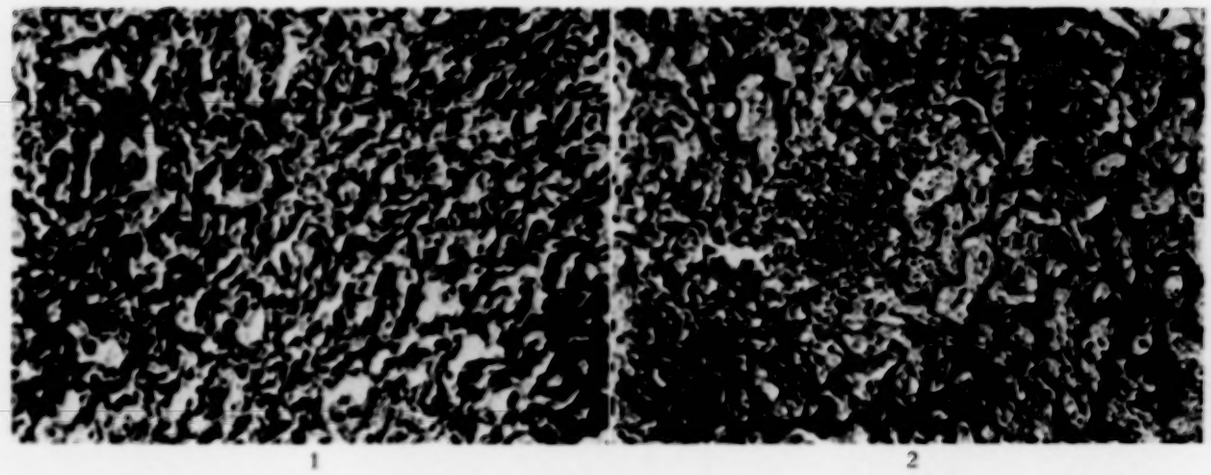

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FIG. 1. Liver cell atrophy, dilatation of sinusoids and disruption of reticulum architecture in urethane-induced hepatic damage. Wilder reticulum-alum hematoxylin stain, original magnification × 250.

FIG. 2. Liver cell atrophy and accumulation of erythrocytes and fibrin in dilated sinusoids, centrilobular zone. Hematoxylin and eosin stain, original magnification × 250.

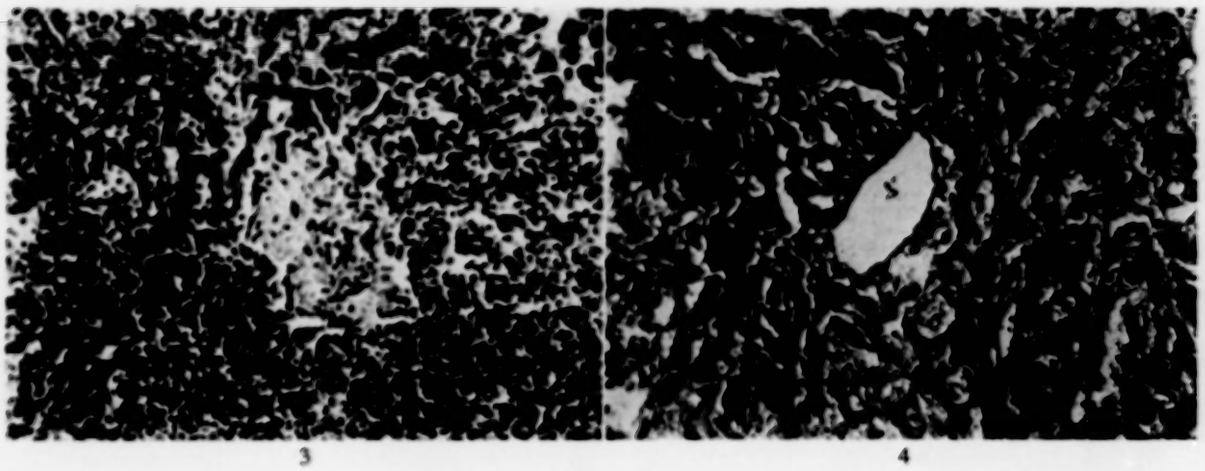

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FIG. 3. Swelling and fragmentation of central veins of the liver lobule associated with severe centrilobular congestion. The endothelial lining of the vein is discontinuous. Hematoxylin and eosin stain, original magnification × 250.

FIG. 4. Extension of liver cell atrophy to the periportal zone with preservation of some periportal cells. Hematoxylin and eosin stain, original magnification × 250.

extrahepatic biliary tree was patent; the gallbladder was slightly distended and filled with viscid greenish yellow bile. All tissues were icteric.

The vertebrae, sternum, ribs, long bones of the extremities and calvarium contained irregular areas of bone destruction with replacement by soft, friable, glistening tumor nodules with a slight greenish tint. There were pathologic fractures of the right humerus, right femur and seventh left rib. The kidneys, spleen and lymph nodes were not significantly altered.

Other findings included left ventricular hypertrophy, small bilateral pleural effusions, focal slight atherosclerosis, mild arteriolar nephrosclerosis, adrenal cortical and thyroid adenomas, and a uterine fibromyoma. The brain was grossly normal.

On microscopic examination the architecture of the liver was found to be distorted by irregular zones of hemorrhage, most of them located in the central portions of the liver lobules. The walls of many central veins were indistinct due to swelling and fragmentation. The sinusoids in the hemorrhagic zones were distended and packed with erythrocytes. The liver cords were atrophied, compressed, and, in places, dissociated from each other. Occasionally, the congestion and hemorrhage extended into the midzonal and periportal areas. In non-hemorrhagic areas the parenchyma showed pale-staining central zones and some distortion of the lobular pattern due to the fact that some liver cells and cords were atrophied and others were undergoing degeneration.

TABLE I
URETHANE DOSAGE IN PATIENTS WITH HEPATIC DAMAGE AND FATAL TERMINATION

Case No.	Total Urethane Dosage before Signs of Hepatic Damage (gm.)	Dose Schedule	Interval from Onset of Urethane Therapy to Hepatic Damage
	Patients with Myeloma		
1	2,259	3 gm. daily, increased to 6 gm. daily for last 4 mo.	21 mo.
2	700	0.64 gm. 3 times daily	12 mo.
3	144	3 gm. daily	48 days
4	?	2 to 4 gm. daily	10½ mo.
5	308	2 gm. 2 times daily	77 days
	Patients without Myeloma		
6	297	9 gm. daily	39 days
7	2,500 (approx.)	(soaked dressings)	4 days

In these areas there was widening of the sinusoids, and intrasinusoidal deposition of a pink staining granular material. The spaces of Disse were widened and prominent. There was fragmentation and disruption of the reticulum fibers in the lobules. Diapedesis of erythrocytes was also present about some of the interlobular vessels. A leukocytic response was practically absent in all areas of the liver. The liver cells which escaped injury were those located at the periphery of the lobules near the portal triads. (Figs. 1 to 4.)

The trabecular architecture of the bone was destroyed and replaced by masses of typical myelomatous cells. Fibrous callus infiltrated by the tumor cells bridged the fracture sites. The residual marrow was hypocellular, with dilated sinusoids and scattered accumulations of fat cells.

The tubules of the kidneys were the seat of a large accumulation of bile casts, leucine crystals, and some hyaline casts associated with compression of adjacent tubular epithelial cells. No amyloid was demonstrable in the kidney but paramyloidosis was noted in the periadrenal vessels and the smaller vessels in the myocardium.

The pathologic diagnoses were multiple myeloma; hepatitis due to urethane therapy; cholemic nephrosis; paramyloidosis; pathological fractures of the seventh left rib, right humerus and femur; hypertensive cardiovascular disease; arteriolar nephrosclerosis, mild; bilateral hydrothorax; slight generalized atherosclerosis; cortical adenoma, left adrenal; colloid adenomatous goiter; and uterine fibromyoma.

ANALYSIS OF REPORTED DATA

A review of the literature has yielded a total of eight cases of hepatic damage associated with urethane therapy in which adequate clinical, laboratory and pathological data are available. Of these six patients died and two recovered after clear-cut evidence of damage to the liver. Multiple myeloma was the primary diagnosis in four

TABLE II*
DATA ON HEPATIC DAMAGE IN FATAL CASES

Case No.	Time Interval from Onset of Hepatic Disease to Death (days)	Thymol Turbidity Test	Cephalin Flocculation Test	Serum			Prothrombin Time (%)	Bromsulphalein Retention	Icterus Index
				Total Bilirubin (mg./100 ml.)	Direct Bilirubin (mg./100 ml.)	Alkaline Phosphatase (Bodansky units)			
				Patients with Myeloma					
1	13	Normal	3+++	20	13	7.2	27	.....	.....
2	5	1.1	Normal	0.51	0.33	13.6	.....	13% in 45 min.	.....
3	1			No Data Reported					
4	4	.....	.....	6.6	.....	.....	.....	.....	.....
5	13	2.5	.....	17.6	9.8	17.3	Normal	62% in 20 min.	50
				Patients without Myeloma					
6	6	.....	.....	Jaundice		Increased	.....	.....	.....
7	7	.....	.....	Jaundice		.....	25	47% in 2 hr.	5.6

* Additional data: Case 1—Total cholesterol 102 mg./100 ml.
Case 5—SGO transaminase 105 units.

TABLE III

URETHANE DOSAGE IN PATIENTS WITH NON-FATAL HEPATIC DAMAGE

Case No.	Total Urethane Dosage before Signs of Hepatic Damage (gm.)	Dose Schedule	Interval from Onset of Urethane Therapy to Hepatic Damage
8	1,275	Dosage not reported; treatment 14 mo.	18½ mo.
9	160	Dosage not reported; treatment 8 wk.	10 wk.

of the reported fatalities and in the two patients who survived the episode of hepatic damage. The two non-myeloma fatalities included one patient with prostatic carcinoma and one with multiple severe burns in whom topical urethane was employed. Data from these eight cases and those from the presently reported case are tabulated in Tables I through V.

The sources of the case reports are as follows: Case I reported by Ohler, Houghton and Moloney [*2*]; Case II by Meacham, Tillotson and Heinle [*3*]; Case III by Hazlett, Taylor and Whitelaw [*4*]; Case IV by Flanagan [*5*]; Case V is the case herein reported; Case VI by Huggins, Yu and Jones [*6*]; Case VII by Levy and Duke [*7*]; Cases VIII and IX by Rundles, Dillon and Dillon [*8*]. In Cases VI and VII the subjects were non-myeloma fatalities; Cases VIII and IX were non-fatal instances of damage to the liver in treated multiple myeloma.

The amount of urethane administered before the onset of clinical evidence of hepatic damage varied widely in the fatal cases, the smallest total dose being 144 gm. (Table I.) Similarly, the duration of treatment varied widely. If the massive dosage administered by the percutaneous route in Case VII is not considered, the interval between onset of treatment and the appearance of damage to the liver ranged from thirty-nine days to twenty-one months. Case VII should probably be considered as an example of acute toxicity, unlike the others.

Examination of the chemical evidence of hepatic damage and the incidence of jaundice in the fatal cases (Table II) demonstrates that abnormal liver function was recognized prior to death in all but one case. Jaundice was absent in two of the seven fatal cases.

TABLE IV

DATA ON HEPATIC DAMAGE IN NON-FATAL CASES

(Maximum Chemical Evidence of Hepatic Damage)

Case No.	Thymol Turbidity	Total Bilirubin (mg./100 ml.)	Alkaline Phosphatase (Bodansky units)	Bromsulphalein Retention
8	Negative	2.8	10.6	Slight, 30 min.
9	Negative	1.1	....	Slight, 45 min.

TABLE V

PATHOLOGIC DESCRIPTION OF HEPATIC DAMAGE

Case No.	Weight (gm.)	Gross Description	Microscopic Description
	1,960	Small subcapsular hemorrhages; parenchyma deep purple-red; lobular markings indistinct	Acute diffuse centrilobular hemorrhagic necrosis; fibrin thrombi in a few central veins and in the sinuses around occluded central veins (slight cirrhosis also present)
2	2,050	Firm; parenchyma mottled yellow-brown; lobular pattern preserved	Centrilobular cell atrophy, necrosis, vacuolization; large sinuses contain pink material and clumps of erythrocytes. Subintimal edema, fragmentation and necrosis of the walls of central veins and portal blood vessels
3	2,100	Surface mottled red and yellow; normal consistency; parenchyma had exaggerated nutmeg appearance; several small areas pale and apparently bloodless	Massive centrilobular hemorrhagic necrosis. Remaining peraportal cells vacuolated. Reticulin framework of liver intact. Central veins obscured so that angionecrosis could not be seen
4	1,350	Consistency firm; parenchyma coarse, red to gray-yellow; indistinct lobular markings	Extensive centrilobular necrosis extending to midzonal and periportal zones with hemorrhage. No sinusoidal endothelium or vascular wall damage
5	990	Congested; soft; parenchyma friable, bile stained, irregular areas of congestion and softening; lobular pattern indistinct	Centrilobular cell atrophy, necrosis, with hemorrhage. Dilated sinusoids filled with fibrin and erythrocytes. Central vein wall fragmentation. Reticulin framework of lobules disrupted
6	.....	.....	Patient died of hepatic necrosis
7	.....	.....	.....
8	.....	.....	Biopsy: central and midzonal hepatic degeneration and fibrosis
9	.....	.....	Biopsy: centrilobular hemorrhage or severe congestion and parenchymal degeneration

In the two non-fatal cases reported with proved hepatic damage, the total dose of urethane and the duration of treatment prior to

the recognition of damage to the liver are comparable to those in the fatal cases. (Table III.)

Clinical jaundice was recognized in Case VIII; in Case IX it was suspected on the basis of nausea and upper abdominal discomfort that parenchymal damage had developed. (Table IV.)

The data on plasma protein levels before and during the period of clinical hepatic damage are inadequate for analysis. Two cases in which such data are available indicate a fall in total plasma proteins but no essential change in the electrophoretic pattern. The total protein in Case I (fatal) fell from 12.1 gm./100 ml. to 6.3 gm./100 ml.; in Case IX (non-fatal) the fall was from 8.4 to 1.5 gm./100 ml. It cannot be determined whether this fall was due to damage to the liver or was the result of other factors in the course of treatment.

Because of the comparatively rare incidence of hepatic damage following urethane therapy, it is necessary to review the other therapeutic modalities which were employed to exclude other potential hepatotoxic agents before urethane is incriminated. The agents of known hepatotoxicity which were employed before the onset of damage to the liver were: methyltestosterone (Case I), adrenal cortical steroids (Cases III, IV, V), and blood transfusion (Cases V, VII, VIII).

The similarity of the pathologic changes in all cases in which such studies are reported indicates that either a single agent was responsible for them all, or that the distribution and type of hepatic damage represents the final common pathway of hepatotoxicity for a number of different agents. The usual pathologic findings in methyltestosterone jaundice, namely centrilobular cholestasis and periportal and periductular inflammation, are strikingly different from those seen in the cases reported. The usual fatty changes of the liver seen with administration of adrenal steroids and the changes of the liver in homologous serum hepatitis are unlike those seen in the reported cases.

COMMENTS

Krogh and Harrop [*9*] used urethane to produce capillary dilatation and stasis of capillary flow by direct application to the tongue of a frog. They ascribed this action to arteriolar constriction, and not to any specific effect of the narcotic on the capillary wall, with increase in endothelial permeability as a primary phenomenon. They described migration of colloidal vital red from the capillaries acutely dilated by the action of urethane, but noted that red cells remained within the vessels. Landis [*10*] concluded that the effect of urethane was related to direct injury to the capillary wall rather than by the mechanism proposed by Krogh and Harrop [*9*].

Doljanski and Rosin [*11*] injected 1 to 5 ml. of a 10 per cent aqueous solution of urethane into young albino rats and found that animals dying within a few minutes after injection showed "extravasation of blood plasma around the branches of the portal veins and marked pericapillary edema." Survival for several hours after injection was accompanied by extravasation of formed elements through the vascular walls, damage to the blood sinusoids especially in the centrilobular areas, and centrilobular liver cell vacuolization and dissociation. With repeated administration of urethane the most prominent changes were seen in the central portions of the liver lobules. The blood sinusoids were often detached from the liver cords and their continuity was frequently interrupted. There was both congestion and extravasation of plasma and formed elements. Degenerative and atrophic changes were seen in the corresponding liver cells. Erythrophagocytosis by liver cells was also noted. They concluded that the vascular changes in urethane poisoning predominated and that vascular and liver cell changes were correlated temporally and geographically.

Mostofi and Larsen [*12*] found evidence of hepatocellular damage, but no endothelial injuries, in rats fifteen to thirty minutes following a single intraperitoneal injection of 25 mg. of urethane in aqueous solution. No lesion of the liver was seen in rats ten to fifteen months after the cessation of long term administration of a narcotizing dose of urethane.

Berman and Axelrod [*13*] described hemosiderin laden macrophages in the periportal regions in a biopsy specimen of the liver following long term urethane treatment of leukemic reticuloendotheliosis, recalling the location of the hemorrhages described by Doljanski and Rosin [*11*], although the possibility of histiocytic migration was not considered.

These studies tend to support the thesis that the damage to the liver which has been described in human subjects after long term exposure to urethane is due to the combined vascular and hepatocellular toxicity of the drug. The major difficulty with this interpretation lies in the relative rarity of clinical evidence of damage to

the liver in patients receiving urethane and in the acute nature of the hepatic damage following massive dosage of the drug in animals as compared with the late and irregular appearance of damage to the liver in man. Only Case VII, in which the patient received about 2,500 gm. of urethane by application to a burned surface and in whom signs of hepatic damage developed within four days, can be considered to be comparable to the acute experiments described in animals.

The synergistic effect of liver toxins may account for some of the observed changes in human subjects. Lushbaugh and Storer [*14*] demonstrated that sublethal amounts of urethane and chloroform, given together, are additively synergistic and can cause death from hepatic injury. This phenomenon may have played a role in Case I, in which methyl testosterone was administered with urethane. It is noteworthy that the pathologic changes in that case were similar to those in which urethane was used alone and were not those pathologic changes of methyltestosterone.

The accumulated data on urethane-induced hepatic failure in man suggest two alternative explanations: (1) either there is a variable susceptibility to urethane among individuals, in the form of an individual idiosyncrasy which may appear during treatment, or (2) urethane hepatitis will occur when the body can no longer metabolize the drug at a rate adequate to maintain subtoxic concentrations.

The site of urethane degradation is presumed to be the liver, with excretion of the resultant products, carbon dioxide, ethanol and ammonia, via the lung and kidney. Inability to degrade urethane presupposes functional hepatic damage for which there is no substantial evidence in the data available on human subjects. However, it is likely that the mechanism of acute urethane hepatitis in animals and in man after sudden administration of massive doses of urethane is due to the discrepancy between the functional capacity of the liver and the urethane load applied to it. In the cases in man characterized by long term urethane therapy and by the sudden appearance of hepatic damage late in the course of treatment, the course is more suggestive of an idiosyncrasy which developed during treatment.

CONCLUSION

A case of hepatic damage associated with urethane therapy is reported and the relevant literature is reviewed. The relationship of the administration of the drug to the appearance of the lesion is examined and the pathogenesis is discussed. It is suggested that the appearance of hepatic damage during long term urethane therapy is an expression of an idiosyncrasy to the drug developed during treatment and not a direct effect of drug toxicity.

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Thalassemia Major*

Thirty-Five Year Survival, with Obliterative Pulmonary Endarteritis and Atypical Bone Changes

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Since the description of thalassemia major by Cooley and Lee in 1925 [*1*], this disease was believed to occur only in children and to result in death before adolescence. March, however, in a review of thalassemia in 1952, reported patients surviving into the fifth decade [*2*]. The present report describes the clinical picture, hematologic studies and postmortem findings in a well documented case of thalassemia in an adult of North European origin. This patient, who was followed up at this hospital for thirty years, presented the unusual features of survival to the age of thirty-five, obliterative pulmonary endarteritis and atypical bone changes.

CASE REPORT

J. H. T., a thirty-five year old white man, was first seen at the University of California Hospital in 1928 at the age of six years because of recurrent chills and fever, jaundice, splenomegaly, and anemia of two years' duration. He was markedly anemic; the hemoglobin was 7.5 gm. per 100 cc. and a blood smear showed increased numbers of normoblasts and reticulocytes, basophilic stippling, and conspicuous anisocytosis and poikilocytosis. When the patient was nine years old a splenectomy performed at another hospital resulted in a modest rise in hemoglobin, which persisted for six months before decreasing to the presplenectomy levels. By the age of thirteen the patient had received twenty transfusions. Thereafter he consulted physicians infrequently, and was not seen again at this hospital until his final admission on March 11, 1958. During this interval his only medication had consisted of small oral doses of iron taken intermittently. At the time of an operation for removal of a gallstone performed when the patient was thirty years old the liver showed gross changes suggestive of cirrhosis. A year later a right medial malleolar ulcer developed which required several months to heal. During the six months preceding admission to this hospital the patient had progressive exertional dyspnea, ascites, peripheral edema, testicular atrophy, loss of axillary hair, loss of libido, and impotence. Four months before hospitalization he had a pathologic fracture of the right radius.

The patient, an only child, was of North European stock. His parents were of Danish-German and Scottish-English-Dutch descent. His father, who had died at the age of forty-seven of "heart-disease," had no history of anemia. His mother, a seventy-five year old woman who is still living, has had a lifelong history of hypochromic anemia unresponsive to iron therapy. A diagnosis of thalassemia minor in the mother was supported by the presence of microcytes, hypochromia, target cells, poikilocytosis and basophilic stippling in blood smears, increased deposition of hemosiderin in the bone marrow, and an A_2 hemoglobin content of 5 per cent (normal 2.5 per cent) as measured by starch block electrophoresis [*3–5*].

At the time of hospitalization the patient was a malnourished prematurely aged man with muddy yellow skin and scleras, mongoloid facies, and pulsating distended neck veins. Physical examination showed generalized cardiac enlargement with loud pulmonic systolic and diastolic murmurs, split second heart sound with accentuation of the pulmonic component, a large, tender, pulsating liver, spider angiomas over the upper part of the trunk and arms, ascites, absent pubic and axillary hair, testicular atrophy, bilateral medial malleolar ulcer scars, and generalized bone tenderness.

The results of laboratory tests were as follows: Packed cell volume, 21 per cent; hemoglobin, 4.9 gm. per 100 cc.; erythrocyte count, 2,150,000 cells per cu. mm.; leukocyte count, 13,400 cells per cu. mm.; platelets, 200,000 per cu. mm.; reticulocytes, 28 per cent; normoblasts, 70,000 per cu. mm. The mean corpuscular volume was 98 cubic microns; mean corpuscular hemoglobin, 22.8 $\mu\mu$g.; and mean corpuscular hemoglobin concentration, 23.4 per cent.

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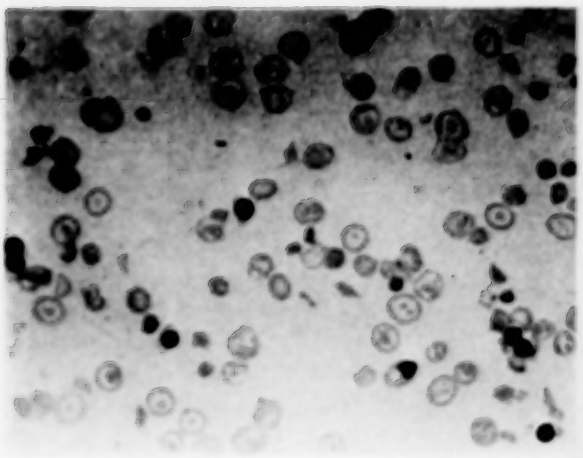

FIG. 1. Peripheral blood smear showing normoblasts, target cells, hypochromia, poikilocytosis, anisocytosis.

A blood smear showed numerous target cells, normocytes, microcytes, macrocytes, anisocytes, poikilocytes, and associated polychromasia, basophilic stippling and Howell-Jolly bodies. (Fig. 1.) Advanced hyperplasia of the erythroid series and increased amounts of hemosiderin were noted in bone marrow smears. Erythrocyte fragility tests demonstrated increased resistance of the cells to hemolysis in hypotonic saline solution; hemolysis began at 0.48 per cent (same in control) and was complete at 0.14 per cent (0.28 per cent in control). Erythrocyte survival time, as measured with Cr^{51} was four days (normal, twenty-seven to thirty-eight days). Erythrocyte cholinesterase was 2.1 units (normal 0.8 to 1.2 units). The concentration of fetal hemoglobin was 11 to 14 per cent; no other abnormal hemoglobins were present. A sickle cell preparation was negative. The serum iron was 216.5 μg. per 100 cc., and total iron binding capacity was 329.2 μg. per 100 cc. Results of liver function tests were as follows: serum bilirubin, prompt direct, 4.0 mg. per 100 cc.; indirect, 4.5 mg. per 100 cc.; total, 8.5 mg. per 100 cc.; total protein, 6.9 gm. per 100 cc.; albumin-globulin ratio, 2.9:4.0; thymol turbidity, 9 units; cephalin flocculation test, 4 plus in forty-eight hours; prothrombin concentration, 34 per cent. The fasting blood sugar was 77 mg. per 100 cc. The circulation time, arm to tongue, was seven seconds. The venous pressure was 210 mm. H_2O pressure. An electrocardiogram demonstrated right axis deviation and probable right ventricular hypertrophy. A biopsy specimen of skin showed melanin pigmentation.

Radiologic survey of the bones showed generalized skeletal demineralization, most obvious in the long bones. A striking feature was the disproportionate involvement of the skull and extremities; the skull appeared normal (Fig. 2), whereas the extremities showed rarefaction and dilatation of the medullary cavities, associated with pronounced cortical thinning. (Figs. 3A and B.) The right radius and ulna, the

FIG. 2. Normal appearance of skull; diploe are of normal width and inner and outer tables are intact.

right fifth rib and left tenth and eleventh ribs showed evidence of recent pathologic fracture.

All manifestations of the patient's illness could be related directly or indirectly to the primary disease process. He was severely anemic, had progressive high output congestive heart failure, and moderately severe hepatic cirrhosis as demonstrated by liver function tests and biopsy. The course was rapidly downhill. The patient died on April 8, 1958, less than one month after admission to the hospital.

At postmortem, extensive bony demineralization and bone marrow hyperplasia with replacement of both cortical and trabecular bone were found. The diploic spaces of the skull were not increased in size. The liver weighed 2,600 gm. and contained 10.9 gm. of iron (normal, 300 mg.). The lobular architecture was obliterated with hepatic parenchymal nodules of varying sizes which were separated by bands of fibrous tissue containing large numbers of bile ducts. The hepatic parenchymal cells were heavily loaded with hemosiderin, and smaller amounts were present in the Kupffer cells. The heart weighed 560 gm. All chambers were dilated; both ventricles were hypertrophied, the right ventricle to a relatively greater degree. Only occasional myocardial fibers contained hemosiderin deposits. The branches of the pulmonary arteries and arterioles showed considerable intimal fibrosis and luminal narrowing. (Fig. 4.) Pulmonary vascular thrombosis could not be demonstrated by gross or microscopic examination or by a postmortem pulmonary arteriogram. The quantitative iron content of the lung was 29 mg. per 100 gms (normal, 25 to 50 mg. per 100 gm.). The lymph node. were enlarged and contained large amounts of hemo-

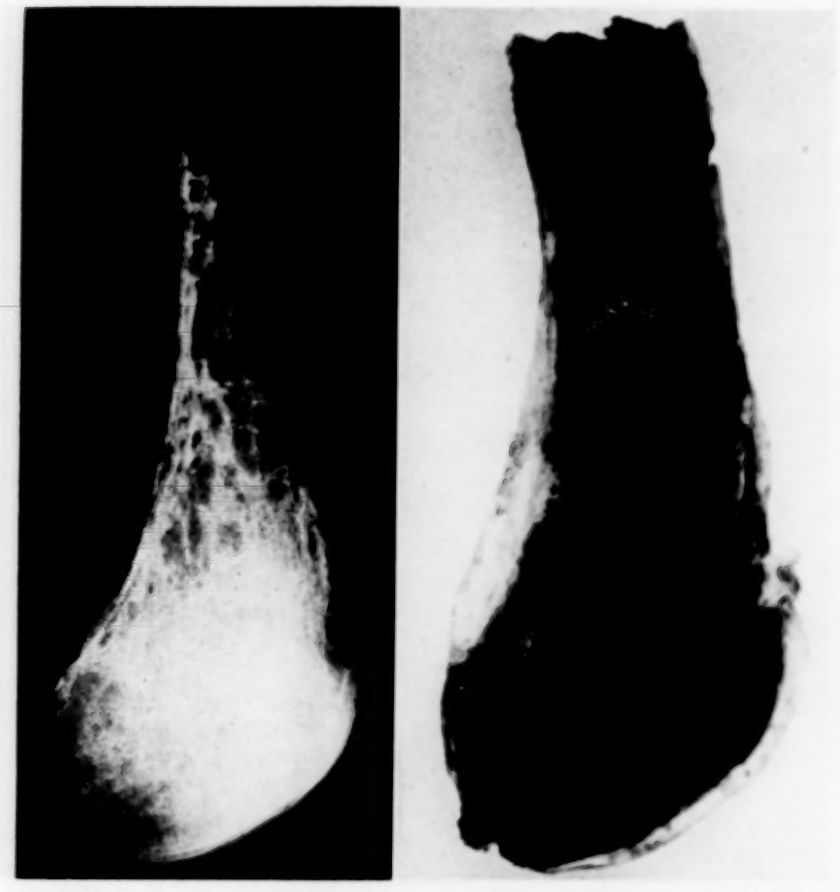

FIG. 3. Left, roentgenogram of autopsy specimen of the distal femur showing rarefaction and dilatation of the medullary cavity associated with pronounced cortical thinning. Right, cross section of distal femur showing marked marrow hyperplasia.

siderin, but showed no evidence of active hemopoiesis. Considerable hemosiderin was present in the acinar cells of the pancreas, but only a small amount in the islet cells. The adrenals were reduced in size, having a combined weight of 8.5 gm. (normal, 12 gm.). Moderate amounts of hemosiderin were deposited in the distal and proximal convoluted tubules and in the loops of Henle. The testes were atrophic and contained moderate amounts of hemosiderin. Large deposits of hemosiderin were found in the gastric mucosa.

The clinical diagnosis of thalassemia major with hemochromatosis and high output congestive heart failure was confirmed on the basis of the following criteria: (1) severe refractory anemia, beginning in childhood, (2) hepatosplenomegaly, (3) increased resistance of red blood cells to hypotonic saline solution, (4) increased fetal hemoglobin (11 to 14 per cent), (5) family history of thalassemia minor, (6) presence of target cells, normoblasts, microcytes, macrocytes, polychromasia, basophilic stippling and Howell-Jolly bodies in blood smears, (7) marked erythroid hyperplasia and increased iron deposits in the bone marrow, (8) cirrhosis and hemosiderosis of liver, (9) rapid circulation in the presence of increased venous pressure.

COMMENTS

Thalassemia, a hereditary disease, is manifested in the heterozygous state as benign thalassemia minor and in the homozygous state as the more severe thalassemia major. The many gradations between the two states are generally believed to represent varying degrees of gene penetrance. Thalassemia major is usually associated with severe, refractory anemia, periodic fever, splenomegaly, hepatomegaly and death at an early age. Thalassemia minor is associated with microcytosis, hypochromia and slight to moderate anemia. The main distinction between the two lies in the severity of the anemia. The disease was originally thought to be limited to the land areas bordering on the Mediterranean,

but recently it has been described in widely scattered areas throughout the world [*1–16*].

Sturgeon and Finch [*17*] concluded that the hematologic abnormality in thalassemia is not a true primary defect in hemoglobin synthesis but a defect in the fabrication of the erythrocyte, resulting in hypochromia, increased content of fetal hemoglobin within the erythrocyte, and a shortened red cell survival time. Rich [*18*] suggested that the basic abnormality is an enzymatic defect blocking the production of normal adult hemoglobin and promoting the continued production of fetal hemoglobin. Red cell survival studies [*20*] have indicated that the accelerated destruction of circulating red cells is a contributory cause of the anemia, but that the major abnormality is in red cell production.

This case illustrates several features which are unusual in thalassemia major, i.e., survival to age thirty-five, North European racial origin, the presence of obliterative pulmonary endarteritis and cor pulmonale, and atypical bone changes.

Although the survival of patients with thalassemia major to adult life has been reported, the percentage of such cases is extremely small, reflecting our inability to offer any substantially beneficial therapy, despite recent advances in knowledge of the disease.

The incidence of thalassemia major in persons of North European racial origin is very low. Thalassemia major has been reported in a few children of North European racial stock, but to our knowledge our case is the first instance reported in an adult.

The extensive pulmonary obliterative endarteritis demonstrated at autopsy has not been previously reported in thalassemia. A postmortem pulmonary arteriogram failed to demonstrate thrombosis in any vessel of the pulmonary vascular bed, as is frequently observed in sickle cell anemia. It is possible that the increased pulmonary blood flow associated with the high cardiac output state prior to the onset of congestive failure and the later development of left ventricular failure raised the pulmonary artery pressure and thus produced secondary obliterative changes. However, objective evidence for such a phenomenon could not be obtained.

The roentgenographic finding of severe demineralization of the bones of the extremities without involvement of the skull in this case is not characteristic of the disease in patients who survive to adulthood. Caffey [*19,20*] noted

FIG. 4. Pulmonary obliterative endarteritis with extensive intimal fibrosis leading to narrowing of the lumen of the small pulmonary artery branches.

a tendency toward greater involvement of the skull than of the long bones in patients past adolescence, and related this to the fact that the red marrow in the more peripheral parts of the skeleton is replaced at an early age with fatty marrow, whereas the red marrow in the skull, spine and pelvis persists throughout life.

Hemochromatosis was diagnosed on the basis of large deposits of hemosiderin in the liver associated with clinical and pathologic evidence of advanced hepatic cirrhosis. Probably the twenty blood transfusions administered before the patient was thirteen years old, in addition to the intermittent small oral doses of iron, resulted in deposition of some hemosiderin. However, it is likely that the severe hemolytic process was responsible for most of the hemosiderin deposited in the liver, since it is believed that over 100 blood transfusions are required to produce extensive transfusion hemosiderosis [*21*]. The severity of the hemolytic process is reflected in the very short erythrocyte survival time of four days (normal, twenty-seven to thirty-eight days) as measured by the Cr^{51} method, a finding in

accord with the data reported by other observers [*17,21*].

SUMMARY

A case of thalassemia major in a subject of North European origin is reported. The unusual features in this case were survival of the patient to the age of thirty-five, the presence of obliterative pulmonary endarteritis, and atypical bone changes.

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Right Atrial Myxoma*

Diagnosis During Life; Successful Surgical Removal

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In 1951 Prichard [*1*] introduced his review of the subject of tumors of the heart with the following statement: "Tumors of the heart are rarely diagnosed before autopsy, largely because there is little knowledge of their natural history. Surgical treatment of these neoplasms is virtually unheard of, and the present state of diagnosis is far behind the therapeutic possibilities. The most common primary tumor has never been diagnosed antemortem; most of the rare antemortem diagnoses have been those of metastatic growths. Several authors have wholeheartedly subscribed to the view that the diagnosis of cardiac tumors is either impossible or a matter of chance." This pessimistic attitude soon proved to be unjustified. In 1952, Kirkeby and Leren [*2*] diagnosed a tumor of the left atrium which at autopsy two days later proved to be a hemangiofibromyxoma. Table 1 lists the cases which have been diagnosed and treated up to the present time.

The availability of surgical technics for the successful removal of benign tumors of the heart makes early diagnosis of great importance. All of the patients heretofore reported on who have undergone surgery, even those successfully operated upon, have had prolonged periods of antecedent cardiac decompensation, which have increased the hazards of surgical intervention. When one considers that these atrial myxomas arise in otherwise normal hearts, the significance of early diagnosis is even more apparent. The most difficult part of the diagnosis seems to be an awareness of the possibility of benign tumor of

TABLE 1
OPERATIONS FOR PRIMARY INTRACAVITARY TUMORS OF THE HEART

Reference and Year	Site	Manner of Diagnosis	Result
Goldberg et al. [*3*], 1952	Left atrium	Angiocardiography	Died
Bahnson et al. [*4*], 1953	Right atrium	Angiocardiography	Died
Clowes et al. [*9*], 1954	Left atrium	At surgery for mitral stenosis	Died
Crafoord, C. [*5*], 1955	Left atrium	Angiocardiography	Recovered
Bailey, C. P. [*6*], 1955	Left atrium, 2	Not stated	Died
Bailey, C. P. [*6*], 1955	Left atrium	At surgery for mitral stenosis	Died
Bigelow et al. [*15*], 1955	Left atrium	At surgery for mitral stenosis	Recovered
Scannell et al. [*10*], 1956	Left atrium	At surgery for mitral stenosis	Recovered
Brock, R. [*11*], 1956	Left atrium	At surgery for mitral stenosis	Died
Paquet, E. [*14*], 1956	Right atrium, pulmonary artery	At surgery for mitral stenosis	Died
Paquet, E. [*14*], 1956	Right atrium	Angiocardiography	Died
Paquet, E. [*14*], 1956	Left atrium	At surgery for mitral stenosis	Died
Van Buchem et al. [*7*], 1957	Left atrium, 2	Clinical and cardiac catheterization	Died
Bahnson et al. [*12*], 1957	Left atrium	At surgery for mitral stenosis	Recovered
Chin and Ross [*16*], 1957	Left atrium	At surgery for mitral stenosis	Recovered
Lyons et al. [*8*], 1958	Right atrium	Angiocardiography	Died
Gerbode et al. [*13*], 1958	Left atrium	Angiocardiography	Recovered
Belcher, J. R. [*18*], 1958	Left atrium	At surgery for mitral stenosis	Recovered
Malm et al. [*17*], 1958	Left atrium	At surgery for mitral stenosis	Recovered

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the heart. Once suspected, the diagnosis is relatively easy to prove or disprove.

CASE REPORT

A thirty-eight year old white man consulted an otolaryngologist, Dr. Lester Coleman, on September 22, 1958, because of episodes of "dizziness," associated with syncope on one occasion. Dr. Coleman found no evidence of disturbed labyrinthine function or other otolaryngological abnormality that might account for the patient's symptoms. The patient was referred to me that same afternoon.

During the preceding two or three weeks the patient had been experiencing episodes of illness which recurred in a constant pattern. These occurred while the patient was lying on his back in bed, usually propped up somewhat, so that he could watch television. First he felt discomfort in the epigastrium, "like a mild blow in the solar plexus." There was slight nausea. Then, in rapid succession, he experienced weakness of the legs, a feeling of heat in the neck and face, shortness of breath, profuse sweating, light-headedness or faintness, and palpitation of the heart. The episodes lasted about two minutes. Sometimes they would pass away spontaneously while the patient continued to lie quietly on his back. However, the patient soon discovered that he could terminate the episodes quite readily by turning on his side, usually the left, but also on the right side, or on his abdomen. A wave-like shock sensation, sweeping through his body from the feet upward, generally informed the patient that the attack was about to terminate. Recovery from each episode was complete, without any sequelae such as weakness, shortness of breath, mental confusion or palpitation. On one occasion, however, the patient got out of bed just as one of his attacks was beginning. After walking one or two steps he fell unconscious to the floor. He was unconscious about one minute and felt perfectly normal upon regaining consciousness. At no time were there any convulsions or incontinence.

Past history revealed malaria in childhood (doubtful), pneumonia at age twenty-two years, and a brief episode of "spastic colitis" associated with a period of unusual emotional tension eight years before. He had not been exposed to any noxious fumes or chemicals. He took no medications.

The family history was not contributory. Systemic review revealed that the patient had had a persistent non-productive cough for several months. He smoked three packs of cigarettes daily and an occasional pipe. (He was advised to stop smoking at the initial visit. He did so, and within two days his cough vanished and never proved to be a significant factor in his illness.) The only other detail uncovered in the system review was dyspnea brought on by unusual exertion such as playing volley ball, or climbing three flights of stairs, during the preceding eight or nine months. None of the attacks which brought him to our attention had occurred during his usual working-day activities.

Physical examination in the office, at the initial visit, revealed a well-developed, overweight (183 pounds, 72 inches tall) man, intelligent, well oriented, cooperative and of placid demeanor. The temperature was normal, respirations were 16/minute, pulse 100/minute, and blood pressure 110/70 mm. Hg. The skin was normal. There was no cyanosis and no venous distention. There were no masses in the neck. The thyroid was not enlarged. The lungs were clear. The heart was not enlarged to percussion or on fluoroscopy. The cardiac rhythm was regular. The heart tones were of good quality and no murmurs were present. Fluoroscopic examination during a barium swallow revealed no esophageal displacement suggestive of chamber enlargement. The abdomen was soft. Liver, kidneys and spleen could not be felt. There were no masses or hernias. The genitalia were normal. Neurologic examination included funduscopy, gross tests of fields of vision, tendon reflexes, Babinski reaction, Romberg test, touch and pin prick. All these tests were within normal limits.

The patient was asked to indicate exactly where the uncomfortable sensation appeared in his abdomen at the onset of his attacks. He placed one finger a little to the right of the midline, in the mid-epigastrium. With a view to exploring the possibility of a pheochromocytoma, the blood pressure cuff was reapplied and the indicated epigastric area was gently massaged. After about fifteen seconds the patient calmly stated, "I think one of these attacks is beginning." Even as he was speaking a purplish blush appeared over the upper 2 or 3 inches of his chest, the neck and shoulders, and the entire head. The nail beds of the fingers were cyanotic, but the forearms and hands were pale, cold and clammy. The torso, legs and feet were slightly pale, with no cyanosis. The feet were cold. The area of the blush rapidly changed from purplish to blue. This was especially noticeable at the ear lobes. Simultaneously, the respirations became rapid and deep but not difficult. The principal effort was applied to inspiration. Expiration was not prolonged. There was no wheezing. No rales appeared in the chest. The blood pressure was not obtainable and the radial pulse could not be felt. However, the heart could be heard beating regularly at a rate of 160 per minute. No murmurs appeared. There were no muscular fasciculations or convulsive movements. The patient responded pertinently to questions during the episode but seemed to be out of contact for three- or four-second intervals several times during its course. The neck and face were covered with perspiration. There were no visibly distended veins, although a diffusely bloated appearance developed on the neck and face during the attack.

The patient was admitted to the hospital on September 23, 1958, with a tentative diagnosis of carcinoid tumor. The attack precipitated by massage

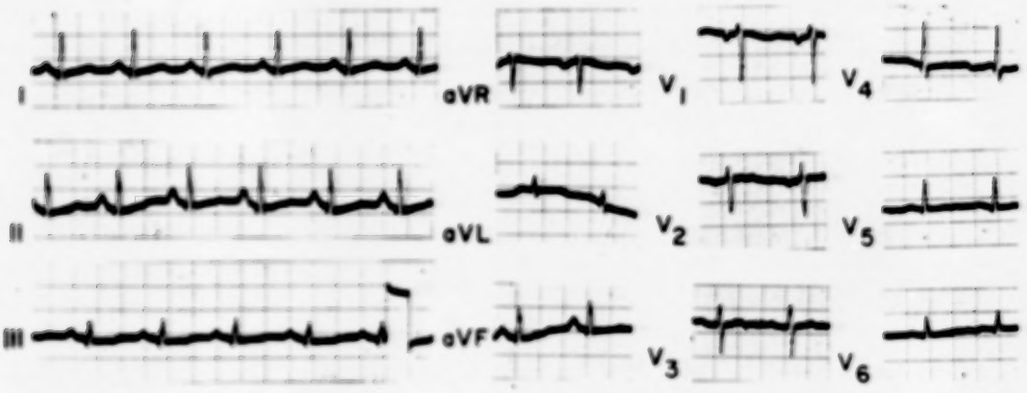

FIG. 1. Electrocardiogram taken September 25, 1958. Peaked P waves in leads II and aVF. Diphasic T waves in leads III, V_2 and V_3. Low T waves in V_5 and V_6.

of the epigastrium suggested that such a tumor might be present in the liver, gallbladder or stomach.

The following laboratory data were obtained: hemoglobin, 14.9 gm./100 ml.; red blood cells, 4,910,000/cu. mm.; white blood cells, 10,000/cu. mm.; 59 segmented forms, 2 non-segmented forms, 30 lymphocytes, 9 monocytes; hematocrit, 47 per cent. The urine had a specific gravity of 1.020, no sugar, a trace of albumin; microscopic examination of the sediment was within normal limits. Fasting blood sugar was 98 mg./100 ml.; inorganic phosphorus of the serum, 3.8 mg./100 ml.; alkaline phosphatase, 2.7 Bodansky units; sodium, 135 mEq./L.; potassium, 5.3 mEq./L.; chlorides, 104 mEq./L. The serum total proteins were 5.9 gm./100 ml.; albumin, 4.0 gm./100 ml.; globulin, 1.9 gm./100 ml.; cholesterol, 158 mg./100 ml.; free cholesterol, 32 per cent. The blood type was AB Rh-positive.

Roentgenograms of the chest, gastrointestinal series, oral cholecystography and barium enema of the colon were all within normal limits. Sigmoidoscopy up to 9 inches revealed no abnormalities.

Electrocardiogram showed a peaked P wave in lead II, diphasic T_3 and very low T waves in all precordial leads. (Fig. 1.) An electroencephalogram revealed normal patterns.

Repeated qualitative tests for 5-hydroxyindolacetic acid in casual and twenty-four-hour urine specimens were negative. One quantitative test revealed 2.4 mg. in twenty-four hours.

In the hospital, the frequency of attacks increased to fifteen or twenty times daily. They occured not only while the patient was lying on his back in bed, but also while he was sitting in a chair. Once, the patient started for his bed when he felt an attack coming on while sitting in a chair in his room but fainted before he could reach the bed. The cyanotic flushing, with all the associated symptoms, could be elicited at will by gentle massage of the epigastrium, either by the examiner or by the patient himself.

It was decided to explore the abdomen for carcinoid tumor. At the time of operation, on October 3, 1958, intubation for anesthesia was very difficult because of an unusually long epiglottis, and because the patient repeatedly became cyanotic and pulseless during the proceedings. Once intubation had been achieved, the anesthesia proceeded smoothly and uneventfully.

Dr. Daniel Casten performed laparotomy. On opening the abdomen about 300 ml. of straw-colored fluid was noted in the peritoneal cavity. The gallbladder was noted and felt edematous. A pedunculated polyp of the jejunum, 5 mm. in size, was palpated. No other abnormalities were detected on thorough exploration. The gallbladder, jejunal polyp and appendix were removed. The gallbladder and appendix were reported as normal. The jejunal polyp was a simple benign mucous polyp.

It became obvious immediately after operation that we had been misled by the effects produced by epigastric massage. Reconsideration of the symptomatology thereupon led us to the diagnosis of a pedunculated tumor of the right atrium which intermittently occluded the superior vena cava. This diagnosis was based on: (1) intermittent attacks of cyanosis confined to the blush area; (2) termination of the attacks by change of position; (3) sudden tachycardia during the attacks, suggestive of a rapid rise in venous pressure (Bainbridge reflex); and (4) the ascites, observed at laparotomy, without hepatic engorgement. It was postulated that during the prolonged periods of cyanosis incident to the difficult intubation immediately prior to laparotomy, increased pressure in the azygos vein had resulted in exudation of fluid into the peritoneal cavity.

Disquieting elements in the diagnosis of intermittent superior vena cava obstruction by an intracardiac tumor were: (1) the absence of any visible venous distention in the neck; (2) the absence of any cardiac murmurs; and (3) the role played by epigastric massage. As to the first point, we had no satisfactory explanation. The patient had a rather thick fleshy neck and this may have obscured some distention of the veins. The absence of any tricuspid

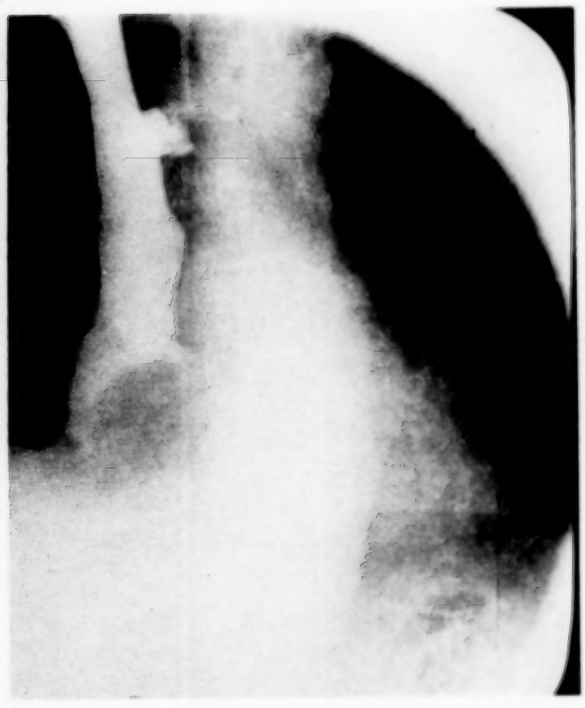

FIG. 2A. The posteroanterior angiocardiogram showing the right atrial area of non-opacification.

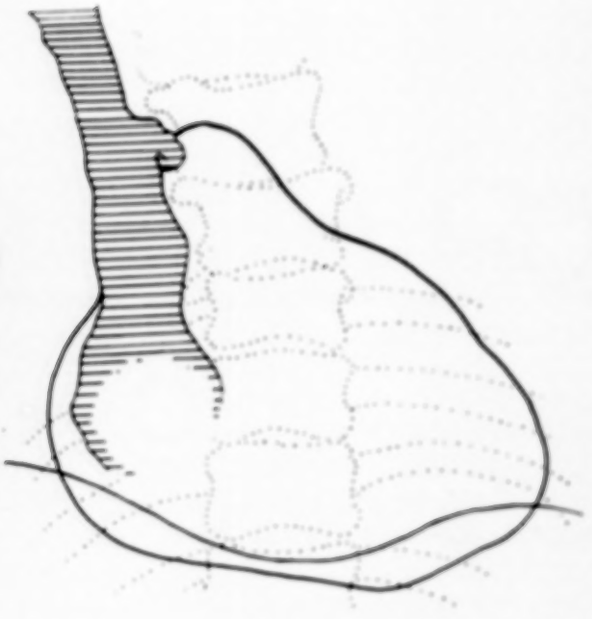

FIG. 2B. Diagram of the angiocardiographic finding.

murmur was consistent with the absence of any edema of the lower extremities and with the normal appearance of the liver at laparotomy. It was difficult to imagine a tumor within the right atrium which could swing on a pedicle in such a way as to occlude the superior vena cava without at some time also occluding the tricuspid valve. However, the clinical evidence indicated that this was indeed the case. An extracardiac tumor could, of course, cause superior vena cava obstruction, but the intermittency of the symptoms, associated with changes in body position, rendered this diagnosis highly improbable. The role of epigastric massage was most difficult to rationalize. A hepatojugular reflux type of mechanism might be evoked. However, it was obvious at laparotomy that there was no appreciable engorgement of the liver or splanchnic veins to constitute a reservoir of blood which might be forced into the right atrium by abdominal pressure. Besides, the degree of pressure generally required to elicit this mechanism was not used. It was nevertheless possible that, even without intra-abdominal venous engorgement, and even without the usual amount of pressure, blood was forced from the abdomen. Perhaps the blood was forced directly from the inferior vena cava into the right atrium in sufficient quantity and with sufficient pressure to displace a pedunculated mass toward the superior vena cava. This would be especially likely to occur during expiration, when the positive intrathoracic pressure would momentarily impede inflow from the superior vena cava.

Postoperatively, on October 3 and October 4, the patient had innumerable attacks of the same nature as before. Oxygen, which had been tried without effect on the attacks preoperatively, still was of no avail. Despite the patient's painful laparotomy wound, he was kept lying on his abdomen. This caused considerable diminution in the frequency of his attacks. However, even in this position the patient noticed that if he sniffed hard, in response to his rhinorrhea, an attack would be precipitated. During one of the postoperative attacks, which lasted about twenty minutes, pitting edema of the forehead was noted. This subsided a few minutes after the attack had terminated. The night of October 4, about thirty-six hours after laparotomy, the patient had his last cyanotic attack. Despite phlebitis of a superficial saphenous vein, in which he had received fluids via a plastic cannula, he made a rapid recovery. Thereafter he could lie in any position, he could sit, walk, strain at stool or bend in any position without recurrence of his cyanotic flushes and their associated symptoms. Auscultation of his heart two or three times daily never revealed any murmurs or arrhythmias. On two occasions a protodiastolic gallop rhythm was heard in the second and third right interspaces, in the parasternal line, lasting only a few minutes.

On October 9, 1958, the venous pressure in a right antecubital vein was 135 mm. of saline solution. The Decholin® circulation time was nineteen seconds; ether circulation time was fifteen seconds. On October 10 anteroposterior and lateral chest laminography was performed. No evidence of mediastinal or intracardiac tumor was detected. The azygos vein was

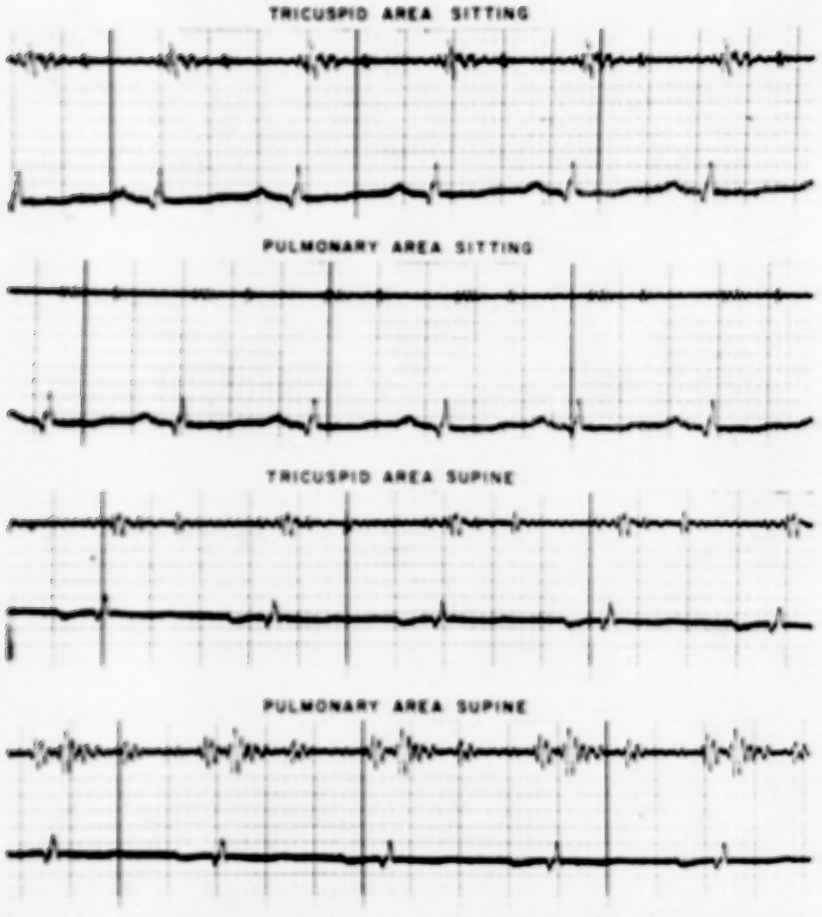

FIG. 3. Phonocardiogram taken October 20, 1958. In the tricuspid area a double systolic sound is apparent with the patient in both the sitting and supine positions. On auscultation this was audible as a systolic gallop only with the patient in the sitting position. Note the appearance of a presystolic gallop rhythm at the pulmonary area with the patient in the supine position. This was occasionally audible as such. Usually, however, a split pulmonic second sound seemed to be present.

reported to be dilated in its anterior course through the mediastinum, at the bifurcation of the trachea, overlying the right main bronchus.

On October 14, 1958, the patient's convalescence from his laparotomy had progressed sufficiently so that he could be transferred to Mount Sinai Hospital for further study. On October 15 angiocardiography was performed and a tumor of the right atrium was demonstrated. (Figs. 2A and 2B.)

The evening of October 14, 1958, was marked by a rise in the patient's temperature. This was associated with a diffuse, tender, painful swelling in the right supraclavicular fossa and the right side of the neck. No masses or thrombosed veins could be delineated. Three blood cultures were taken within a thirty-six-hour period and intensive antibiotic medication was instituted. The blood cultures proved to be sterile. The temperature rose as high as 104°F., subsided by lysis, and reached normal by October 22. During this period the swelling of the neck gradually regressed. This episode was interpreted as a localized phlebitis of neck veins. The absence of any filling defect in the superior vena cava on the angiocardiogram of October 15 was reassuring in indicating that there had been no venous thrombosis by direct extension from the right atrium to the neck.

On October 14 the venous pressure (right antecubital) was 185 mm. in saline solution. The ether circulation time was twenty-two seconds, Decholin circulation time 25 seconds. The blood pressure was 100/80 mm. Hg.

On the evening of October 15, several hours after the angiocardiogram, a cardiac murmur was heard for the first time. This was a presystolic murmur at the tricuspid area, heard while the patient was in a sitting position. P2 was split. The following day, with the patient in the sitting position, a low-pitched presystolic rumble, followed by a short systolic puff, was heard, best in the third and fourth intercostal spaces in the left parasternal line. These murmurs

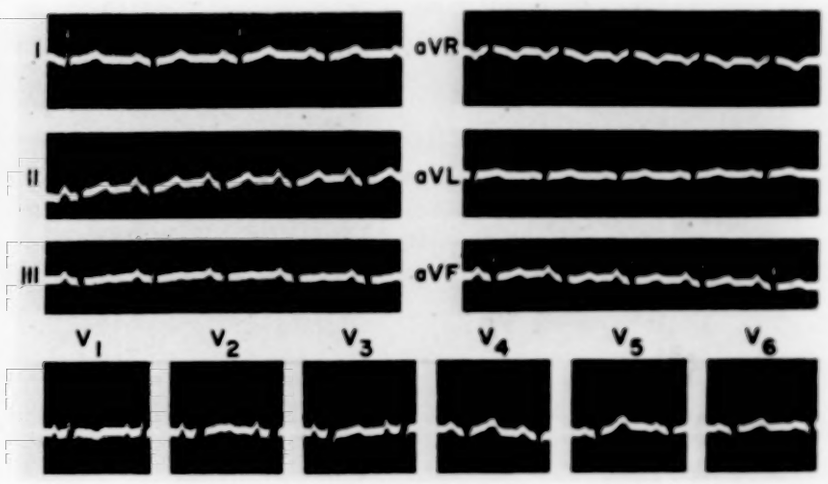

FIG. 4. Electrocardiogram taken October 20, 1958. P waves which were negative in leads V_1 and V_2 on September 25, 1958 are now positive and peaked. The other P waves are also of greater amplitude, as are the T waves.

were transmitted to the aortic area. When the patient assumed the supine position the murmurs could no longer be heard; instead, a systolic gallop could be made out in the third right interspace. In the third and fourth intercostal spaces, near the sternum, the first sound was reduplicated and followed by a lightly tapping second sound. (Fig. 3.)

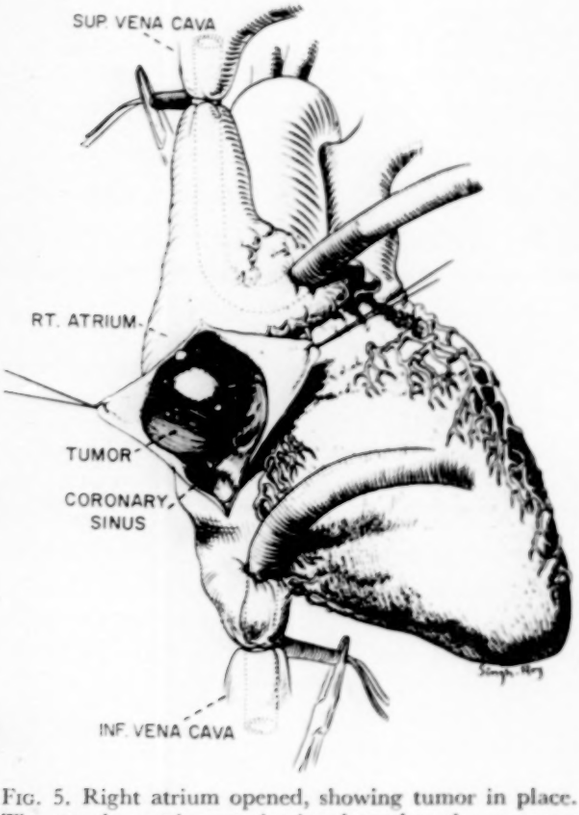

FIG. 5. Right atrium opened, showing tumor in place. The attachment is posterior just lateral to the coronary sinus.

On October 20, 1958, the electrocardiogram showed no significant abnormalities except tall peaked P waves in leads II, V_1, V_2 and V_3. (Fig. 4.)

Surgery was performed on October 23, 1958. The patient was prone throughout the operation. Anesthesia was induced with sodium pentothal and maintained with sodium pentothal, nitrous oxide and Anectine.® The patient was placed on a hypohyperthermia mat for maintenance of body temperature. An indwelling rectal thermometer gave a continuous recording of the patient's temperature. Catheters were placed in the lower inferior vena cava through the saphenous vein and into the aorta through the brachial artery, for constant monitoring of the venous and arterial pressures. Electrodes were placed on the patient's head for continuous recording of the electroencephalogram. Continuous electrocardiography was also set in operation.

A bilateral transsternal incision into the chest was made through the fourth intercostal space. An incision was made over the left femoral artery for insertion of the arterial cannula. Immediately after the rib-spreader was inserted into the chest, the anesthesiologist noted marked flattening in the electroencephalogram. This was followed by disappearance of the arterial blood pressure. Several of these episodes, lasting fifteen to thirty seconds, occurred before the pericardium was widely opened. After opening the pericardium it was obvious that a large mass in the right atrium was intermittently prolapsing into the area of the tricuspid valve. Because of the patient's unstable condition, heparin (2 mg./kg. of body weight) was quickly given and the arterial return catheter was inserted into the femoral artery. Immediately thereafter large catheters were inserted into the venae cavae through the right atrium. The patient was connected to the pump oxygenator which had previously been prepared and primed with fresh

FIG. 6A. The tumor after its removal. The dark areas represent hemorrhages within the substance of the tumor. The arrow points to an irregular whitish area which is the short pedicle by which the tumor was attached to the atrial wall.

FIG. 6B. The tumor bisected and laid open. The dark areas represent hemorrhages.

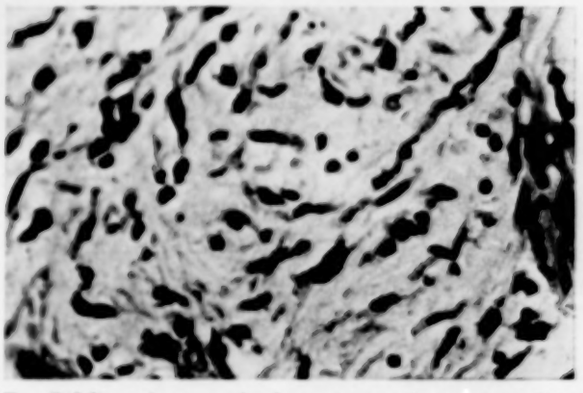

FIG. 7. Microphotograph of a representative section of the tumor.

blood. The pump was turned on and when blood balance between the patient and the machine was achieved, the right atrium was widely opened. A large, well encapsulated mass filled the atrium, attached by a short pedicle to the lateral wall. (Fig. 5.) This was easily removed. The atrium was allowed to fill and the incision in the atrium was closed. The pump was then turned off.

The total perfusion time was fifteen minutes, at flow rates of 60 to 70 ml./kg./minute, with maintenance of normal arterial pressure and electroencephalogram. Protamine (4 mg. kg. of body weight) was given to neutralize the heparin, and the chest was closed. The patient's vital signs remained perfectly stable following extracorporeal circulation and he was returned to the recovery room in excellent condition.

Convalescence proceeded quite satisfactorily. The patient was out of bed on the fourth postoperative day. On the twelfth postoperative day the patient experienced a transient episode of weakness. He passed two loose tarry stools and sustained a sharp drop in hemoglobin level. There were no abdominal symptoms. Two units of blood restored the patient's hemoglobin to a satisfactory level. One week following the episode of tarry stools, roentgenograms of the gastrointestinal tract revealed no abnormalities. The patient was discharged from the hospital in excellent condition on November 14, 1958, the twenty-second postoperative day. He had no murmurs or arrhythmias. He returned to his usual (sedentary) occupation on December 8, 1958.

The extirpated tumor (Figures 6A and B) was described by Dr. Sadao Otani as follows: The specimen consisted of a well encapsulated, oval, plum-sized mass measuring 6 cm. in greatest diameter. The capsule was smooth, thin and fibrous. There was a defect of the capsule, approximately 1 cm. in diameter, in the center of the mass. This area appeared to be the site of the attachment to the endocardium. Section of the mass revealed it to be composed of a soft, tannish yellow gelatinous tissue with scattered hemorrhagic areas. On microscopic examination (Fig. 7) the tumor was found to consist of elongated spindle-shaped fibroblast-like cells in a mucoid matrix. Star-shaped cells were occasionally seen. The cellularity differed in different locations. Arteries of varying size were evenly distributed throughout the tumor. The larger arteries showed a conspicuously hypertrophic muscular wall. Scattered foci of hemorrhage and iron pigment deposition were seen.

COMMENTS

The available case reports of intracavitary myxomas of the heart have been reviewed with the aim of selecting from them a group of findings which might suggest the correct diagnosis at an early stage. Since angiocardiography will establish the diagnosis with very little risk to the

patient, a clear concept of the early manifestations may spare future patients many months or years of disability prior to definitive surgery.

In some cases [*3,6*] the earliest manifestations of left atrial myxoma have been cerebral or peripheral embolization; it is probable that pulmonary embolization from right atrial myxoma will eventually be reported as a primary manifestation. Grand mal seizures may occur, without any residual paralyses. These events may direct attention to the heart only when there are associated cardiac findings. Murmurs may appear to suggest rheumatic heart disease, but a history of rheumatic fever or of antecedent cardiac abnormalities is lacking. In this connection, it is important to remember that isolated tricuspid stenosis is rare in rheumatic heart disease and should of itself suggest right atrial tumor. Also, embolization in rheumatic heart disease is unusual without auricular fibrillation. Subacute bacterial endocarditis may be suggested by the cardiac murmurs, embolic phenomena and the mild fever which has been reported in some cases of left atrial myxoma. However, the blood cultures are negative, there is absence of splenomegaly, anemia and petechiae, and the auscultatory findings are variable (as will be discussed subsequently).

Intracardiac tumors may be too small to cause symptoms [*17,20*]. When the tumor has attained sufficient size to impede the flow of blood into one of the atria, or from one of the atria into a ventricle, and yet is small enough to move readily on its pedicle, the earliest localizing manifestations are likely to occur. These will depend on the location, the degree and the duration of the mechanical obstruction. The patient may seek medical advice because of syncope, or because of episodes of unaccustomed dyspnea not necessarily related to exertion, or because of episodic palpitation occurring with air hunger, weakness and faintness. Any of these symptoms should evoke inquiry concerning their relation to changes in body position. The patient may make this correlation as part of his presenting complaint. For example, he may be dyspneic when sitting and relieved when recumbent or, as in our case, subject to attacks of air hunger, cyanosis, palpitation and weakness while in a supine position, and relieved when in a prone position. Also, an episode of dyspnea, wheezing, cough and weakness may be precipitated by bending over to tie a shoelace.

Unlike the usual situation in progressive valvular or myocardial disease, severe symptoms of acute cardiac disorder may alternate with prolonged periods of apparent good health. Indeed, the absence of abnormal physical findings may cast doubt on the organic origin of the patient's complaints. However, if the patient is observed during one of the crises which has impelled him to seek medical help, all such doubt will be dissipated. The patient is dyspneic, cyanotic and prostrate. If the tumor is in the left atrium there is a cough, and rales are heard in the lungs; expiratory wheezing usually are present, and hemoptysis may occur. If the tumor is in the right atrium the lungs are clear, despite air hunger; cyanosis of the head is of a blue-black quality, especially noticeable in the tip of the nose and the ear lobes. In left atrial tumor, gross venous engorgement may be observed in the neck. This sign may also be manifest in right atrial tumor, but in this condition it is more likely that the neck, face and eyes will be diffusely engorged. Pitting edema of the forehead occurs as a transient phenomenon early in the course of right atrial myxoma; in cases of left atrial myxoma it occurs as part of the general picture of cardiac decompensation. The patient's blood pressure, if taken during an asymptomatic interval, is in the low normal range, with a reduced pulse pressure, for example, 110/80 mm. Hg or 95/70 mm. Hg. However, during the attack it is at shock levels or altogether unobtainable and associated with syncope. The extremities are cold and clammy, and the face and neck may be covered with profuse perspiration. An anginal type of pain may be present.

Auscultation of the heart discloses a tachycardia with normal sinus rhythm. There may be no murmurs (as in our case, [*21,22*]), but if none are heard during early attacks they are to be expected in later ones as the tumor enlarges by growth or due to hemorrhage within its substance. In cases of left atrial myxoma the usual finding is a presystolic apical rumble. A thrill is often present. There may be a diastolic crescendo murmur or a late diastolic murmur with no presystolic component. The absence of an opening snap may be helpful in differentiating these murmurs from the sounds produced by stenotic valvular disease. However, a distinct opening snap may occur [*16*]. No diastolic murmurs may be heard, only an apical systolic murmur. The first mitral sound is frequently reduplicated and P2 is usually accentuated. In

cases of right atrial myxoma similar murmurs and reduplication of M1 are heard in the tricuspid area. The characteristic feature of all these murmurs associated with intracavitary myxomas is their variability. They change or disappear and recur from day to day for no apparent reason, or depending on the position of the patient. A frequent finding is a presystolic rumble which disappears and is replaced by a soft systolic apical murmur when the patient alters his position. Because different observers may report diverse auscultatory findings at different times, it is helpful to document the variability of the murmurs with phonocardiograms. The absence of an opening snap may thus also be confirmed.

The venous pressure is generally elevated. In the isolated superior vena cava obstruction presented by our patient, it is probable that the venous pressure in the arms would have been significantly different from that in the legs. However, this investigation was not made.

The arm-to-tongue circulation time is increased. In our patient the entire increase in circulation time occurred in the arm-to-lung component; the lung-to-tongue fraction was, in fact, less than normal. Whether this is a distinguishing characteristic of right atrial tumor, as opposed to left, is not apparent from available evidence.

Van Buchem et al. [*7,22*], in a study of a case of left atrial myxoma, found that "strikingly powerful pulsations of the oesophagus may occur synchronously with ventricular contractions at the level of the left atrium." This was demonstrated by fluoroscopy and recorded by kymography. To produce this sign the tumor would have to be of considerable size and of firm consistency. This phenomenon is absent in enlargement of the left atrium due to mitral stenosis. The fact that Van Buchem's patient had no murmurs at the time this sign was demonstrated suggests that it may have value early in the course of the disease.

On x-ray examination of the chest two other findings may contribute to the differential diagnosis of primary intracavitary tumors of the heart. First, in cases clinically suggestive of mitral stenosis, the degree of dyspnea is strikingly disproportionate to the enlargement of the left atrium. Second, in cases of right atrial myxoma, clinically suggestive of tricuspid stenosis, the lungs are remarkably free of vascular engorgement even with advanced evidence of right heart failure. Otherwise, the roentgenographic findings are not distinctive. The heart may be of normal size and configuration, despite severe symptoms or, various chamber enlargements and straightening of the left border of the heart, consistent with right or left heart failure, may be present. Congestive changes will appear in the lungs if left heart failure exists.

The electrocardiogram may be normal. When changes do occur, they are not specific. Increased amplitude, peaking and notching of the P waves in lead II are the most frequent abnormalities. Similar P wave changes occur in lead III and the precordial leads on the right side of the heart. Tumors of the left atrium generally are associated with electrocardiographic changes indicative of right ventricular hypertrophy. A tumor of the right atrium may also be associated with electrocardiographic signs of right ventricular hypertrophy [*14*]. However, in our case and the one reported by Lyons et al. [*8*] the only significant changes appeared in the P waves. In the latter case, QS waves in V_1 and V_2 were also present. It is possible that the "huge right atrium" displaced the right ventricle downward so that the precordial electrode was really exploring the cavity of the heart, thus producing the negative waves. Such a finding might be anticipated in future cases of right atrial myxoma.

Cardiac catheterization is not of definitive value in the diagnosis of primary intracavitary tumor of the heart. If this diagnosis has already been suggested as a possibility on the basis of signs and symptoms such as we have discussed, it would probably be wiser to spare the patient the additional hazard of cardiac catheterization and proceed directly to angiocardiography. However, in an ill defined case of heart disease, cardiac catheterization studies may contribute appreciably toward the final solution. When an elevated pressure is found in the right atrium, and normal pressures exist in the right ventricle and pulmonary artery, this would indicate atrioventricular obstruction at the tricuspid valve [*4,14*]. If, as pointed out by Bahnson and Newman [*4*], the atrial pressure shows its lowest dip just prior to ventricular contraction, this would argue against tricuspid stenosis and suggest "some valve mechanism which was temporarily relieved between auricular and ventricular contraction." In one case of left atrial myxoma [*22*] increased pressure in the right ventricle and pulmonary artery, consistent with mi-

tral stenosis, suggested the correct diagnosis by virtue of the fact that no murmurs were present.

Malm et al. [*17*] refer to three subjects explored for atrial tumor on the basis of diagnosis by angiocardiography, in which no tumor was found at operation. This experience appears to be exceptional. Short of surgical exploration, angiocardiography is the most reliable means of establishing the diagnosis of intracavitary tumor of the heart. Furthermore, this technic reveals the size and location of the tumor, and may yield clues to the site of its attachment to the atrial wall.

Once heart failure develops as a result of intra-atrial tumor it usually follows a rapidly progressive course. It is characteristically refractory to the usual treatment with diuretics, digitalis, oxygen and bed rest. In fact, it is this very lack of response which may suggest the correct diagnosis for the first time. Sudden death is common, most often precipitated by complete atrioventricular occlusion; sometimes by pulmonary, cerebral or multiple peripheral emboli.

It is noteworthy that attempts to remove intracardiac tumors by closed methods have all resulted in failure. It was not until the use of hypothermia and extracorporeal circulation technics allowed direct vision surgery that successes were achieved. Blind removal of these tumors, either intentionally or when discovered accidentally at the time of mitral surgery, is fraught with the dangers of bleeding, incomplete removal, or dislodgement of tumor particles. With the great improvement, in the past few years, of open methods, these benign intracardiac tumors can be more easily and safely removed.

SUMMARY

A case of right atrial myxoma is reported which was diagnosed clinically, proved by angiocardiography, and successfully removed by open heart surgery. The clinical manifestations of benign left and right atrial tumors are reviewed.

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Remission of Graves' Disease Following Radiotherapy of a Pituitary Neoplasm*

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SEVERAL theories, each supported by some experimental evidence, have been advanced to explain the as yet obscure pathogenesis of Graves' disease. Since thyroid function normally is regulated by the pituitary gland via the thyroid-stimulating hormone (TSH), these theories have implicated either the pituitary gland or the thyroid itself as the locus of the primary abnormality responsible for the disease [*1–4*].

A patient with Graves' disease has recently been observed in whom an expanding lesion of the pituitary gland was also present. Evidence was obtained to suggest that the hyperthyroidism of this patient was related to the pituitary neoplasm. The possible relevance of this case to the etiology of Graves' disease in general prompted the following report.

CASE REPORT

A fifty-one year old Rumanian-born white housewife was admitted to the Columbia-Presbyterian Medical Center in October 1957 with a chief complaint of unilateral exophthalmos of four months' duration. Except for a labile hypertension known to be present for six years, she had been in good health until four months prior to admission, when she noticed that her right eye had become more prominent than the left. She consulted a physician who elicited a history of weight loss of 30 pounds over the preceding nine-month period, associated with an excellent appetite. Two months later, her basal metabolic rate was determined to be plus 28 per cent; a skull roentgenogram, taken at this time because of the persistent exophthalmos, showed an enlarged sella turcica. A visual field examination was normal. Exophthalmometer measurements were reported as 19 mm. in each eye.

In the two months prior to admission, the patient noticed intolerance to heat, increased perspiration and increased emotional lability. Menses had ceased spontaneously fifteen months previously. There was no family history for thyroid disease.

Physical examination showed a blood pressure of 170/90 mm. Hg, pulse rate of 88 per minute and a weight of 160 pounds. The skin was warm and slightly moist; no finger tremor was present. The right palpebral fissure was greater than the left; the right eye appeared proptotic and lid lag was present in this eye. Neither weakness of conversion nor conjunctival suffusion was noted; the fundi were normal. The thyroid gland was only questionably enlarged to palpation, but a bruit was heard over the gland by one observer, and a substernal extension of the thyroid could be palpated, rising from beneath the sternum upon swallowing. Colorless striae were noted over the abdomen. The physical examination was otherwise within normal limits. There were no manifestations of acromegaly.

Laboratory studies revealed a normal sedimentation rate, hemogram and urinalysis. Radioactive I^{131} uptake at twenty-four hours was 55 per cent; following a seven-day course of triiodothyronine (50 μg. per day), a repeat I^{131} uptake was 54 per cent. Other thyroid function studies included a basal metabolic rate of plus 10 per cent, a protein-bound iodine of 8.9 μg. per cent and a cholesterol of 187 mg. per cent.

Determinations of blood sugar, serum calcium and phosphorus were within normal limits. Skull roentgenograms showed enlargement of the sella turcica, including a depressed floor, suggestive of an expanding lesion of the pituitary gland. (Fig. 1.) Roentgenograms of the chest, spine and hands were within normal limits. An intravenous ACTH test was performed, with a pre-ACTH plasma hydrocortisone concentration of 23 μg. per cent, rising to a post-ACTH level of 48 μg. per cent, both values being considered to be in the normal range for this laboratory.

The presence of an expanding pituitary lesion in a patient with Graves' disease led to speculation concerning the possible etiological role of the former condition with respect to the latter. Accordingly, it was elected to treat the pituitary tumor with radiation, and to observe the patient closely for evidence of remission of her thyroid disease. No therapy for the hyperthyroidism was administered other than the course of radiation to the pituitary gland, which

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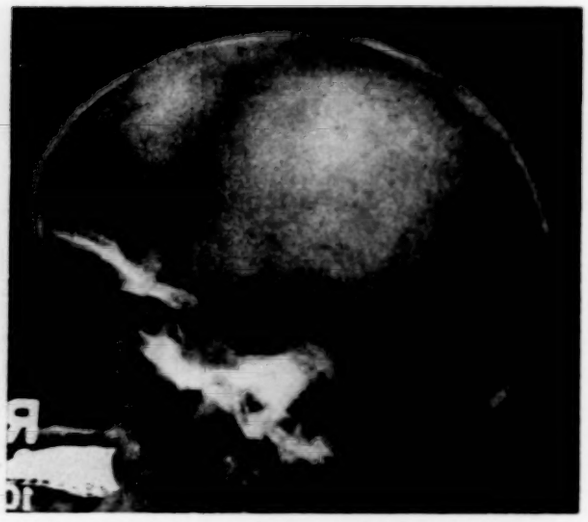

FIG. 1. Lateral roentgenogram of the skull. Note depression and duplication of the floor of the sella turcica and partial erosion of the posterior clinoid processes, strongly suggesting the presence of an intrasellar expanding lesion.

consisted of a tumor dose of 3,560 r delivered through three well shielded ports over a five-week period.

Three months following completion of the course of radiotherapy, the patient had gained 18 pounds and no longer had complaints referable to emotional instability, heat intolerance or excessive perspiration. The unilateral proptosis had remained static. Repetition of the thyroid function tests revealed a radioactive I^{131} uptake of 32 per cent at twenty-four hours, basal metabolic rate of plus 1 per cent, protein-bound iodine of 8.5 μg. per cent and serum cholesterol of 229 mg. per cent. Four months after radiation, the protein-bound iodine had fallen to 7.9 μg. per cent and seven months after radiotherapy it was 6.3 μg. per cent, a value well within the normal range.*

COMMENTS

This patient presented a fairly typical picture of exophthalmic goiter, with symptoms and signs characteristic of the disease. The thyroid function tests confirmed the diagnosis, increased protein-bound iodine, basal metabolic rate and radioiodine uptake all being present. The latter test remained in the elevated range following triiodothyronine administration; the failure of large doses of thyroid extract or triiodothyronine to suppress radioiodine uptake is characteristically present in patients with Graves' disease [6,7].

Convincing clinical remission of the patient's hyperthyroidism occurred following radiotherapy to the pituitary gland. The thyroid function tests also returned to the normal range. While the possibility cannot be excluded that this remission occurred spontaneously, it seems more reasonable to attribute the remission to the pituitary radiation, in view of the temporal association between treatment and clinical improvement.

The markedly elevated serum TSH concentration (as determined by the D'Angelo technic) prior to radiation supports the thesis that the pituitary neoplasm was composed of functional tissue, actively secreting abnormally great quantities of TSH. Stimulation of the thyroid gland by excessive amounts of TSH conceivably produced the thyrotoxicosis manifested by this patient, since it has been shown that administration of TSH to experimental animals and to normal human subjects will produce a syndrome very similar to hyperthyroidism. The sharp fall in serum TSH to near normal levels in the patient following pituitary radiation could reasonably account for the ensuing clinical and laboratory remission of the hyperthyroidism. The fall in serum TSH levels may also account for the rapidity with which the radioiodine uptake returned to normal. On the other hand, the protein-bound iodine returned to the normal range much more gradually.

Review of the literature reveals only a single report, by Hermann [8], of a patient similar to the one presented here. This patient had severe bilateral exophthalmos, mild but unequivocal hyperthyroidism, and radiological evidence of an intrasellar tumor. Pituitary radiation was followed by gradual improvement of the exophthalmos and remission of the hyperthyroidism. A patient reported by Werner and Stewart [9] may be related to the present case. This patient had hyperthyroidism unassociated with ophthalmologic complications and a chromophobe adenoma which was discovered at autopsy. Along with other interpretations, the authors discussed the possibility that the pituitary tumor may have produced large amounts of TSH and thereby caused the patient's thyrotoxicosis.

The occasional association of hyperthyroidism and acromegaly has been known for many years [10,11], and has been considered evidence of TSH elaboration by the growth hormone-pro-

* Serum TSH assays, kindly performed by Dr. S. A. D'Angelo, using the stasis tadpole technic [5], revealed a preradiation level of 1.8 U.S.P. milliunits per cc., falling to a postradiation concentration of 0.7 U.S.P. milliunits per cc. These two TSH concentrations are significantly different; both values are greater than 0.4 U.S.P. milliunits per cc., the upper limit of normal with this technic.

ducing adenomas. D'Angelo et al. [5] measured serum TSH levels in three patients with acromegaly and found these to be considerably higher than normal values. Remission of hyperthyroidism occurring in patients with acromegaly has been reported following either pituitary radiation or hypophysectomy [10].

Other evidence exists suggesting that pituitary tissue may occasionally secrete excessive amounts of TSH. Furth has produced thyrotropin-secreting pituitary tumors in mice by treating the animals with large doses of radioiodine; these tumors are composed of cells which appear to be chromophobic on routine staining, but which are shown to contain granules when stained by the periodic acid-Schiff technic [12]. Russfield et al. have studied a large number of pituitary tumors from patients with acromegaly and also from patients with "chromophobe" adenomas [13]. Both groups of pituitaries contained Schiff-positive granules; clinical and/or pathological evidence in both groups of patients supported the concept that the majority of these tumors were functional, producing one or more of the pituitary trophic hormones.

The vast majority of patients with Graves' disease present no radiologic manifestation of pituitary abnormality. However, there is evidence suggesting a possible etiological role for the pituitary gland in exophthalmic goiter. Albeaux-Fernet et al. reported on a patient with severe hyperthyroidism and exophthalmos in whom hypophysectomy was followed by striking remission of both conditions [14]. Success in the treatment of thyrotoxicosis by radiotherapy of the pituitary gland has been reported in two patients by Hermann [8], in ten patients by Gedda and Lindgren [15] and in twenty-three patients by Thompson and Thompson [16]. Exophthalmos has been successfully treated by hypophysectomy [14,17], transection of the pituitary stalk [17,18] and pituitary radiation [8,15,19]. These reports must be viewed with the important qualification that the various treatments employed may have affected hypothalmic centers as well as the pituitary gland itself.

Attempts have been made to detect elevated TSH concentrations in the body fluids of patients with Graves' disease. The results have been variable and inconclusive, as noted in a recent review of the subject [20]. The recent demonstration by Adams and Purves [21] of an "abnormal" TSH circulating in the blood of such patients has been confirmed [21] and may provide the long postulated link between the pituitary and thyroid glands in Graves' disease.

Coexistent thyrotoxicosis and panhypopituitarism in the same patient would cast serious doubt on the pituitary gland as a primary or even accessory factor in Graves' disease. Two patients with hyperthyroidism and presumed pituitary hypofunction have been reported recently, but convincing clinical manifestations of hypopituitarism were not present in either case. The patient of Werner and Stewart, mentioned previously, had a chromophobe adenoma replacing approximately 95 per cent of her normal anterior pituitary tissue [9]. However, this tumor, or the remaining 5 per cent of normal gland, conceivably could have been a source of increased amounts of normal or abnormal TSH; this patient would then be a close replication of the case reported here. Fajans' patient, who was presented as a case of postpartum necrosis of the pituitary gland, is a questionable example of panhypopituitarism insofar as her menses reappeared when she returned to a euthyroid state and she excreted pituitary gonadotropins intermittently [22]. In many respects her clinical picture suggests anorexia nervosa with coincident thyrotoxicosis, rather than panhypopituitarism.

The reported patient probably represents a case of thyrotoxicosis with non-infiltrative exophthalmos to which a definite etiology can be ascribed, i.e., a pituitary tumor producing excessive amounts of TSH. Extrapolations from this case to the etiology of Graves' disease in general are unwarranted and unwise.

CONCLUSION

A fifty-one year old woman with thyrotoxicosis and unilateral exophthalmos is reported in whom an expanding lesion of the pituitary gland was also present. Following a course of radiotherapy directed to the pituitary lesion, remission of the hyperthyroidism occurred, although no other antithyroid measures were employed. It is postulated that the pituitary tumor in this patient produced excessive quantities of TSH and so was directly responsible for the patient's thyrotoxicosis.

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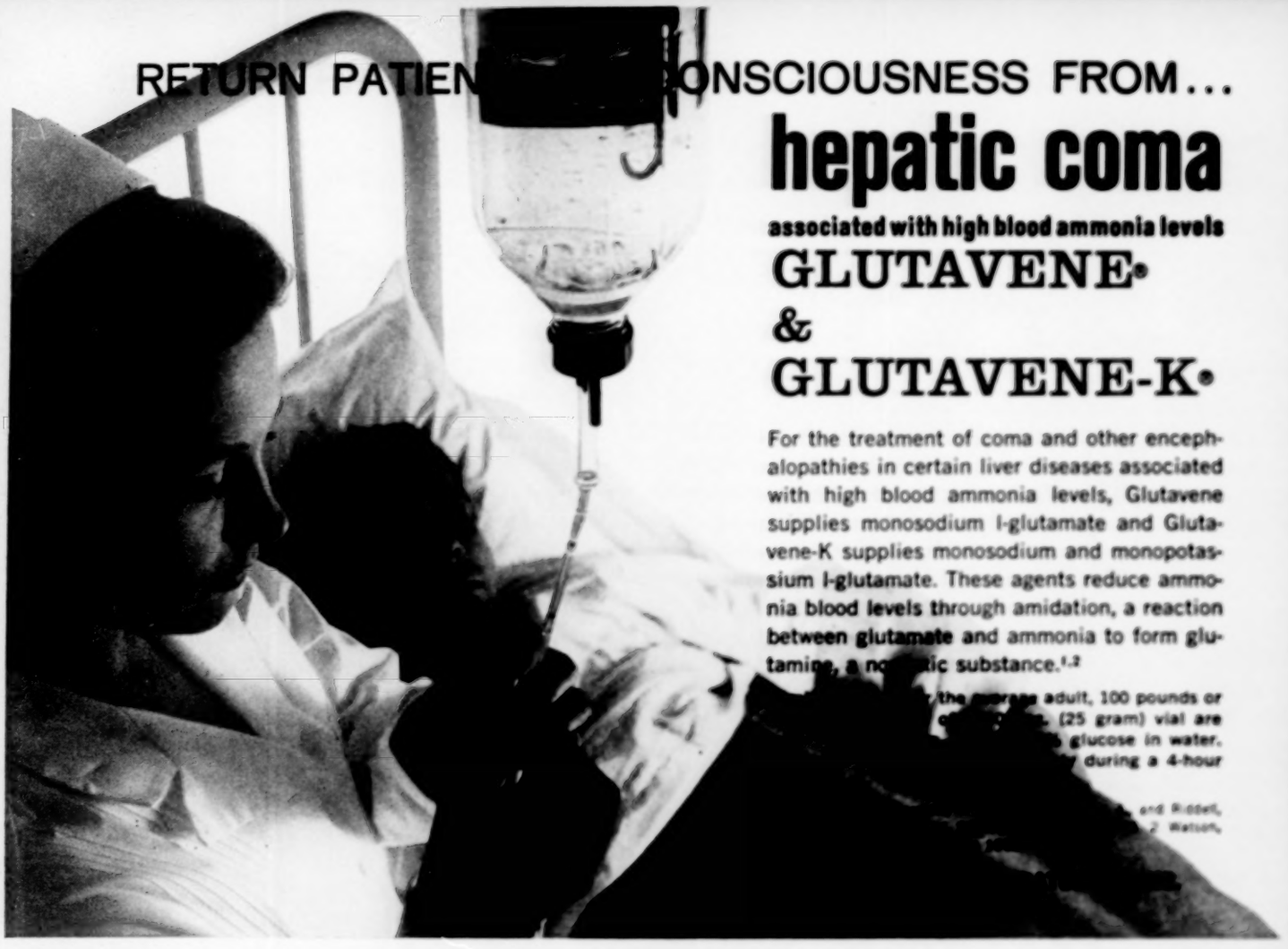

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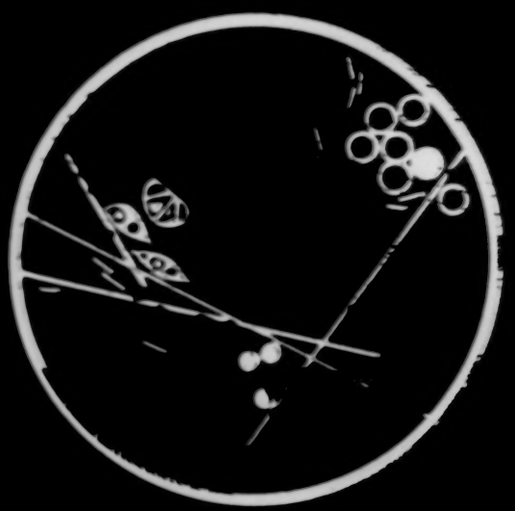

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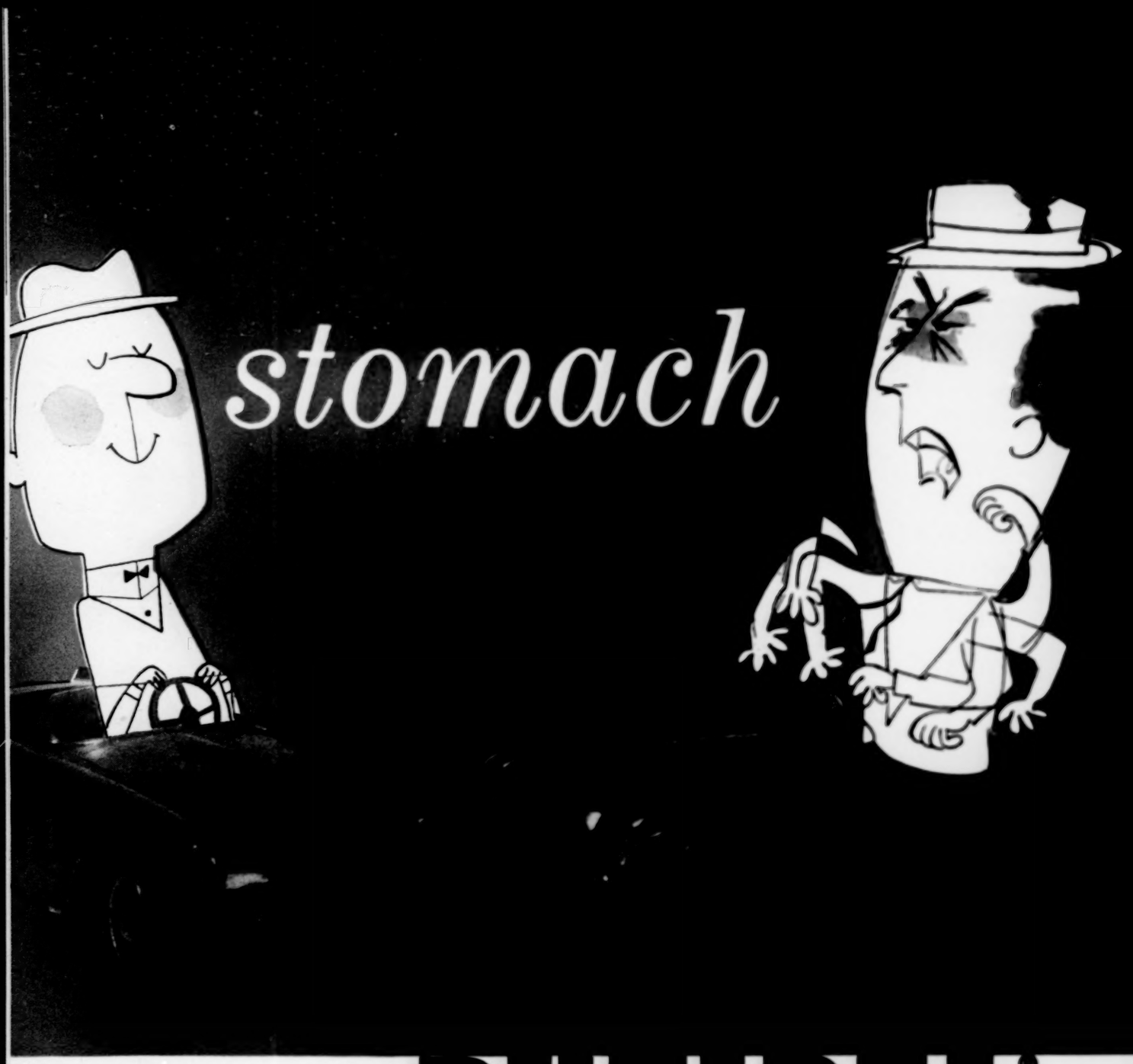

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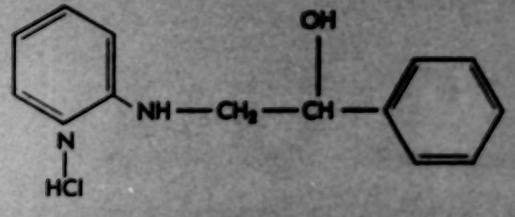

The full chemical name for phenyramidol is 2-(β hydroxy-phenethylamino)-pyridine hydrochloride. It is unrelated to any currently available analgesic or muscle relaxant compound.[3,4]

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The end result of pain, regardless of its origin, is discomfort or suffering paralleled by muscle tension. Thus muscle tension may play a fundamental role in the total pain experience even though it does not initiate the pain. Employment of a single agent that produces two distinct but associated physiologic responses has obvious advantages, for relief of the total pain experience is better accomplished by the integrated action of phenyramidol which acts on both pain centers and muscle to produce analgesia and relieve muscle tension simultaneously.

with remarkably few side effects

Side effects such as sedation, euphoria, mental confusion and depression, sometimes associated with interneuronal blocking and certain analgesic agents have not been noted with Analexin. Incidence of reactions is low and those reactions that occasionally occur (such as gastric irritation and pruritus) are of a mild and transient nature and do not limit therapy.[5]

[redacted]

announcing a new class of drug

analexin

results with analexin in clinical trials

Batterman, Grossman and Mouratoff[5] compared Analexin with aspirin, sodium salicylate and a placebo in a series of 195 patients with various painful conditions. The authors concluded:

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

"Phenyramidol (Analexin), with therapeutic doses is not only safe for chronic administration, but also to date we have noted no adverse effect upon the cardiovascular, gastrointestinal, respiratory, kidney, liver or central nervous systems."

Wainer[6] reported a series of 200 cases treated with phenyramidol for various painful conditions. In fifty of these patients who had dysmenorrhea, he saw excellent results in 40, good results in 5 and poor results in 5. Further examination in 4 cases not responding revealed presence of organic pathology. A second group of 50 cases with headache and associated premenstrual tension responded with over-all excellent results. Wainer also reports the use of phenyramidol to replace codeine for postpartum pain and describes 100 cases wherein a combination of phenyramidol with aluminum aspirin (Analexin-AF) successfully replaced aspirin and codeine therapy.

more results with analexin in clinical trials

In another series of dysmenorrhea cases, Bader[7] compiled data on 20 employees of a telephone company who required ½ to 2 days off from work every month regardless of prior therapy employed. Satisfactory results were achieved in 15 out of 20 and a fair response in the remaining five. All were able to remain on the job although relief was not complete in the latter cases.

Bealer[8] treated 32 patients with phenyramidol mostly for musculoskeletal disorders and had good or very good results in 15, fair results in 14 and poor or inconclusive results in 2 patients. Cohen[9] used phenyramidol together with aspirin in 15 patients with such conditions as sciatic pain, osteoarthritis, anterior chest wall syndrome, etc. and got outstanding relief in 80 per cent. Gilbert[10] reported that 15 patients with nonspecific headache had excellent relief in a matter of minutes with phenyramidol, and in 8 cases of dry socket pain Bruno[11] reports immediate relief in six cases and good results later in the other two after sockets were curetted under local anesthesia. Stern[12] reported on 40 ambulatory cases with a variety of painful conditions and saw good relief in 32 patients and poor in 8. Results were best in acute sacroiliac pain, myositis, muscle spasm, fractures, pleurisy and neuritis. Ten of 13 patients with osteoarthritis responded very well and are continuing on phenyramidol therapy.

Meisler

announcing a new class of drug

analexin

analexin *(phenyramidol)*

for relief of pain *and muscle tension* in:

low back pain
sprains and strains
myalgia
glass arm
wry neck
osteoarthritis
dysmenorrhea
tension headache
gout
postpartum pain
epigastric distress
(pylorospasms, gastritis, duodenal ulcer, cholecystitis)
genitourinary conditions
(premenstrual cramping or tension)
abdominal distress
(flatulence, colic)
toothache and dry socket pain

analexin-AF *(phenyramidol with aluminum aspirin)*

for relief of pain and muscle tension also involving inflammatory processes and/or fever, as in:

arthritis
arthralgia
bursitis
tendinitis
myalgia of strain and tear
pre- and postoperative toothache

dosage:

analexin: for relieving pain and/or muscle tension, one or two tablets every 4 hours. In dysmenorrhea, two tablets initially then one tablet every 2 to 4 hours as needed.

analexin-AF: two tablets every 4 hours or as required.

supply:

analexin tablets—Each tablet contains 200 mg. of phenyramidol HCl. Bottles of 100 tablets.

analexin-AF tablets — Each tablet contains 100 mg. of phenyramidol HCl and 300 mg. of aluminum aspirin. Bottles of 100 tablets.

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Clinical Reports cited above are in the files of the Medical Department, Irwin, Neisler & Co.

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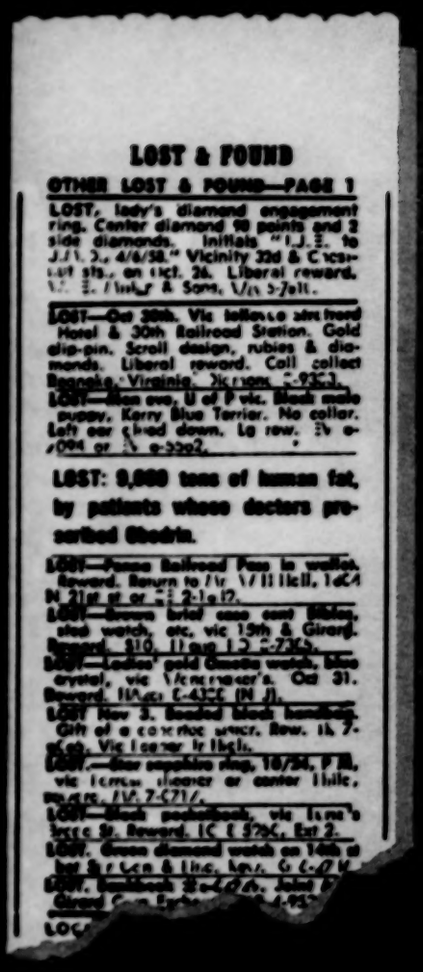

LOST & FOUND

OTHER LOST & FOUND—PAGE 1

LOST, lady's diamond engagement ring. Center diamond 90 points and 2 side diamonds. Initials "I.J.E. to J.J.D., 4/6/58." Vicinity 32d & Chestnut sts., on Oct. 26. Liberal reward. W. E. Hinkle & Sons, Va 5-7611.

LOST—Oct 28th. Via Jefferson Statler Hotel & 30th Railroad Station. Gold clip-pin. Scroll design, rubies & diamonds. Liberal reward. Call collect Roanoke, Virginia, Jackson 3-9363.

LOST—Mon eve, U of P vic. Black male puppy, Kerry Blue Terrier. No collar. Left ear cropped down. Lg rew. Va 6-7094 or Va 6-3202.

LOST: 9,000 tons of human fat, by patients whose doctors prescribed Obedrin.

LOST—Penna Railroad Pass in wallet. Reward. Return to Mr. Williams, 1624 N 21st st or ph 2-1612.

LOST—Brown brief case east Elkins, stop watch, etc, vic 19th & Girard. Reward. $10. Hugo LO 4-7365.

LOST—Ladies' gold Gruen watch, blue crystal, vic Wanamaker's. Oct 31. Reward. Hugo 6-4356 (N J).

LOST Nov 3. Beaded black handbag. Gift of a convention worker. Rew. Ik 7-4760. Vic Leader Filed.

LOST.—Star sapphire ring, 10/24, PTB, vic Temple theater or center Phila, market. JV 7-6711.

LOST—Black pocketbook, vic Penn's Landing Sq. Reward. LO 4-9726, Ext 2.

LOST. Green diamond watch on 16th st bet Spruce & Pine. Kens. GE 6-4[illegible]

LOST. Bankbook 28-[illegible] John F. Glenn Gem Exhibit [illegible]

LOST

Obedrin and the 60-10-70 Basic Plan provide the three essentials of weight reduction:

1	2	3
Supervision by the physician	**A balanced eating plan**	**Supportive medication**

Obedrin curbs unhealthy food craving, enabling the patient to establish correct eating habits . . . first, to lose excess pounds and then, more important, to maintain optimum weight.

Obedrin

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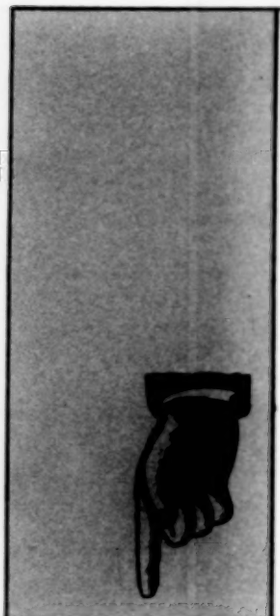
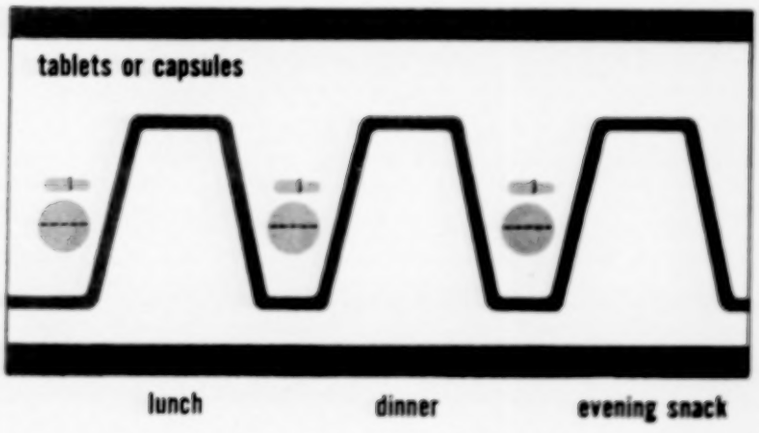
A FLEXIBLE DOSAGE FORM PROVIDES DEPENDABLE CONTROL OF APPETITE





The Obedrin formula permits a flexible dosage schedule to depress the appetite at peak hunger periods. The physician can adjust dosage to fit each patient's need.

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A flexible dosage form!
Minimal central nervous stimulation!
Vitamins to supplement the diet!
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Write for 60-10-70 menus, weight charts, and Obedrin samples. Used with the 60-10-70 Basic Plan, Obedrin offers an ideal weight-control regimen for the overweight patient.

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a smooth, creamy preparation
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to fill any
topical need

Aristocort Acetonide Cream
TRIAMCINOLONE ACETONIDE 0.1%
Tubes of 5 and 15 Gm.

Aristocort Acetonide Ointment
TRIAMCINOLONE ACETONIDE 0.1%
Tubes of 5 and 15 Gm.
Especially desirable in thick lichenified chronic dermatoses requiring frictional application

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NEOMYCIN-TRIAMCINOLONE ACETONIDE 0.1%
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For inflammatory, allergic, infective eye and ear conditions

acceptance...

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Triamcinolone Acetonide-Neomycin LEDERLE

FOAM

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Triamcinolone Acetonide — with therapeutic efficacy equal to *or greater* than that of topical hydrocortisone — in one-tenth the concentration;[1,2] plus neomycin—a leading topical antimicrobial agent.

(2) The Vehicle
NEO-ARISTODERM Foam spreads readily without irritation or burning. It can be applied to oozing, crusted, severely inflamed and injured skin, or to mucous membranes. There have been no reactions of primary irritation or allergic sensitization to date.

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NEO-ARISTODERM Foam *is neat—not messy or sticky*. Patients like the attractive push-button dispenser and the richness of the foam. This helps to assure faithful adherence to your instructions.

Triamcinolone Acetonide 0.1%, Neomycin Sulfate 0.35% 15 cc. Push-button dispenser

References: 1. Kanof, N. B., and Blau, S.: *New York J. Med.* 59:2184 (June 1) 1959.
2. Smith, J. G., Jr.; Zawisza, R. J., and Blank, H.: *A.M.A. Arch. Dermat.* 78:643 (Nov.) 1958.

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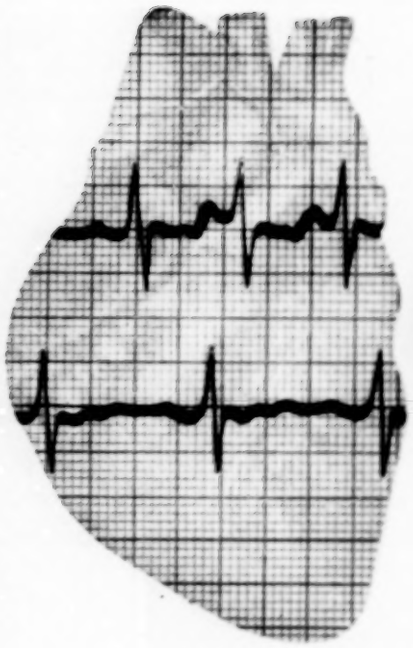

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1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

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(1) Barnes, R. H.: J.A.M.A. *166*:898, 1958. (2) Ressler, C.: J.A.M.A. *165*:135, 1957. (3) Birnberg, C. H., and Abitbol, M. M.: Obst. & Gynec. *11*:463, 1958. (4) Robillard, R.: Canad. M.A.J. *76*:938, 1957.

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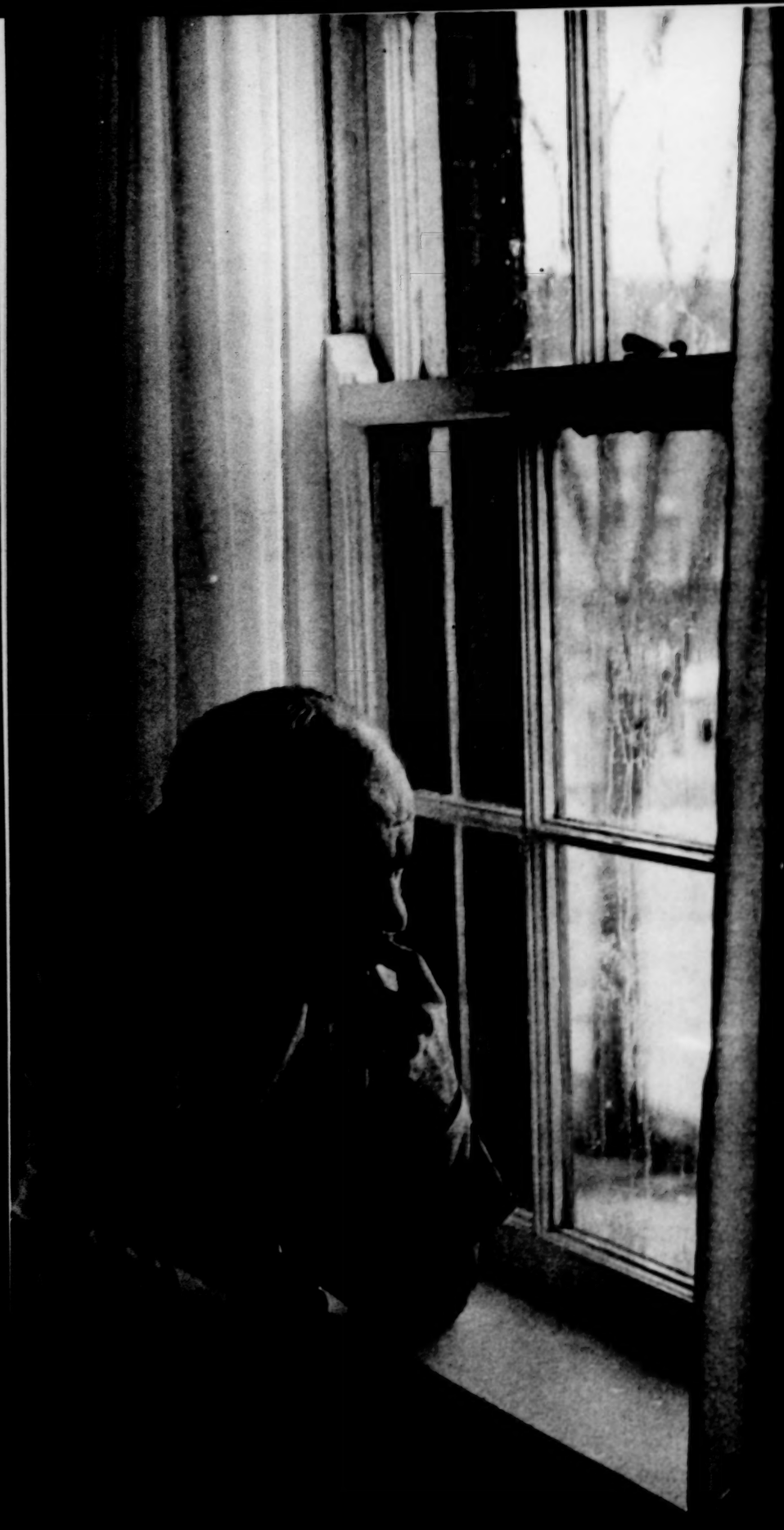

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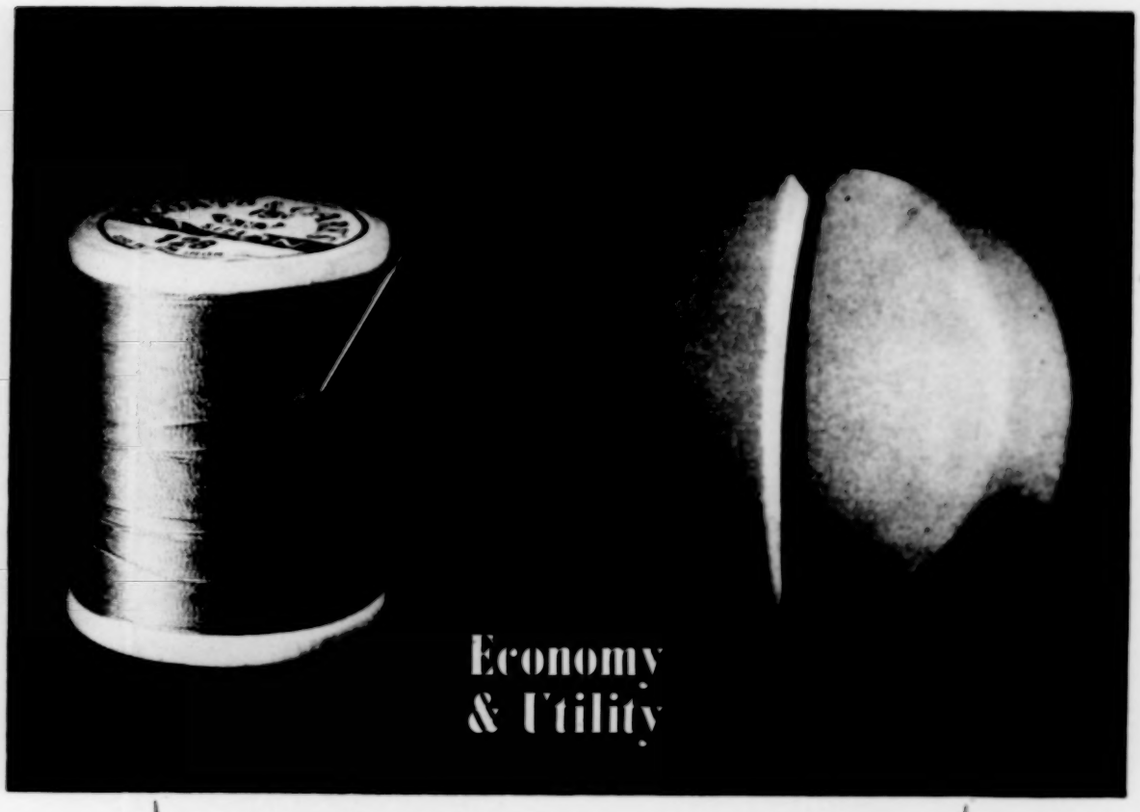

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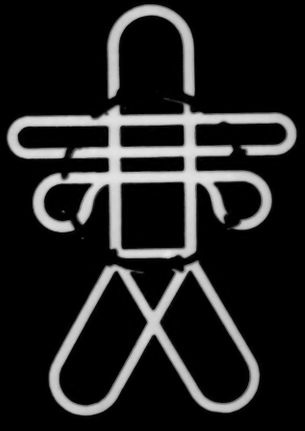

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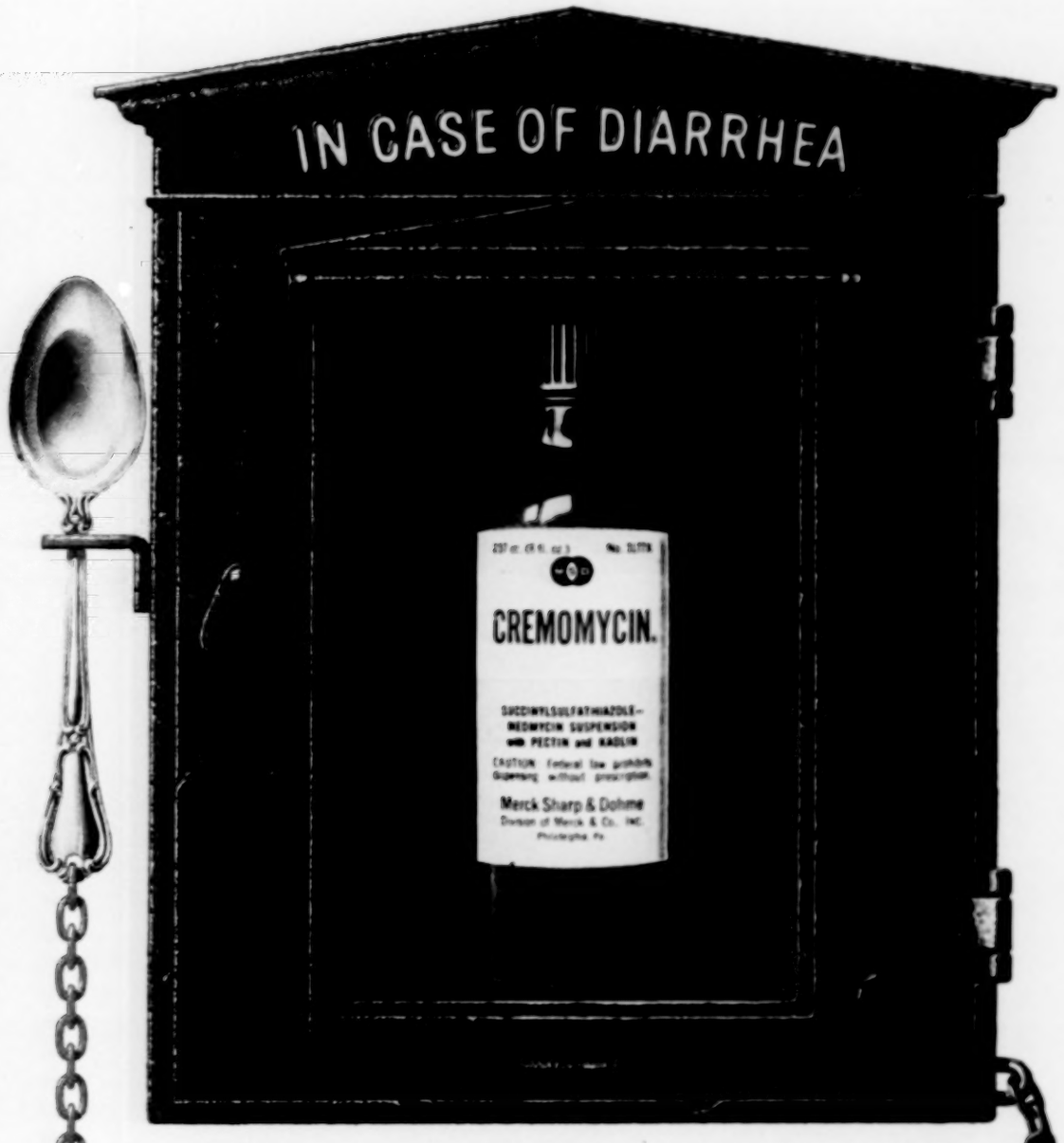

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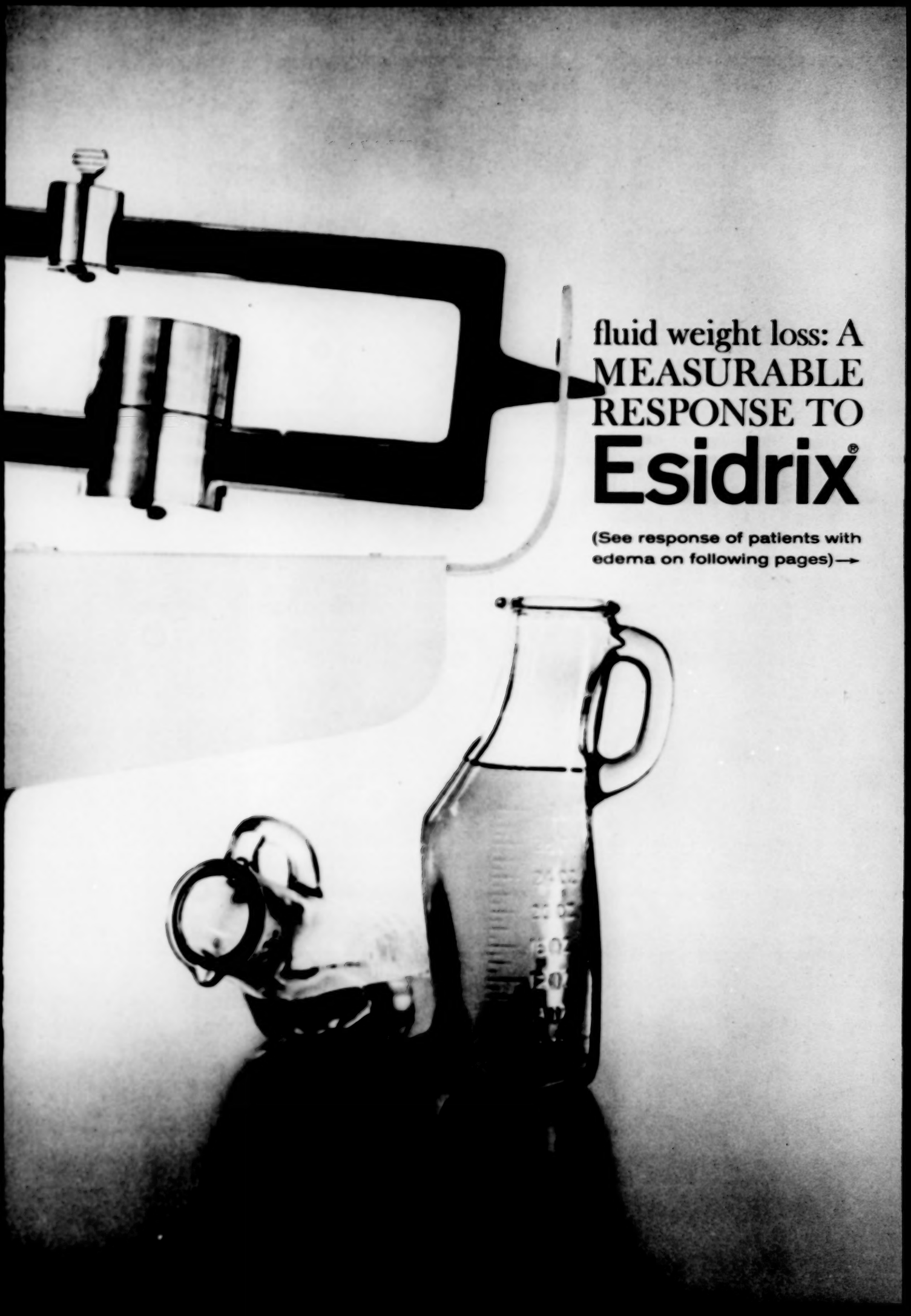

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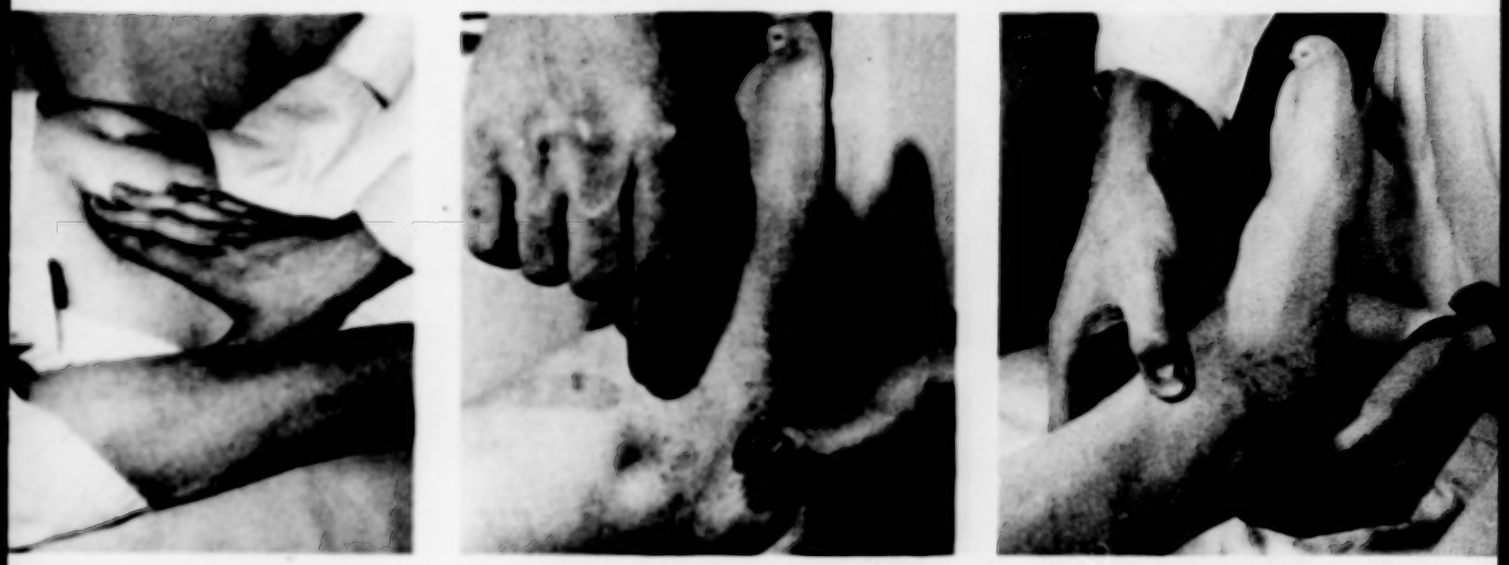

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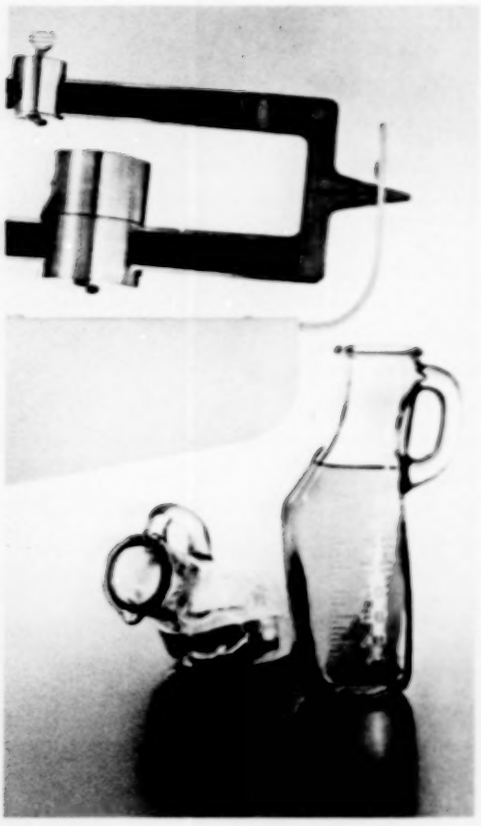

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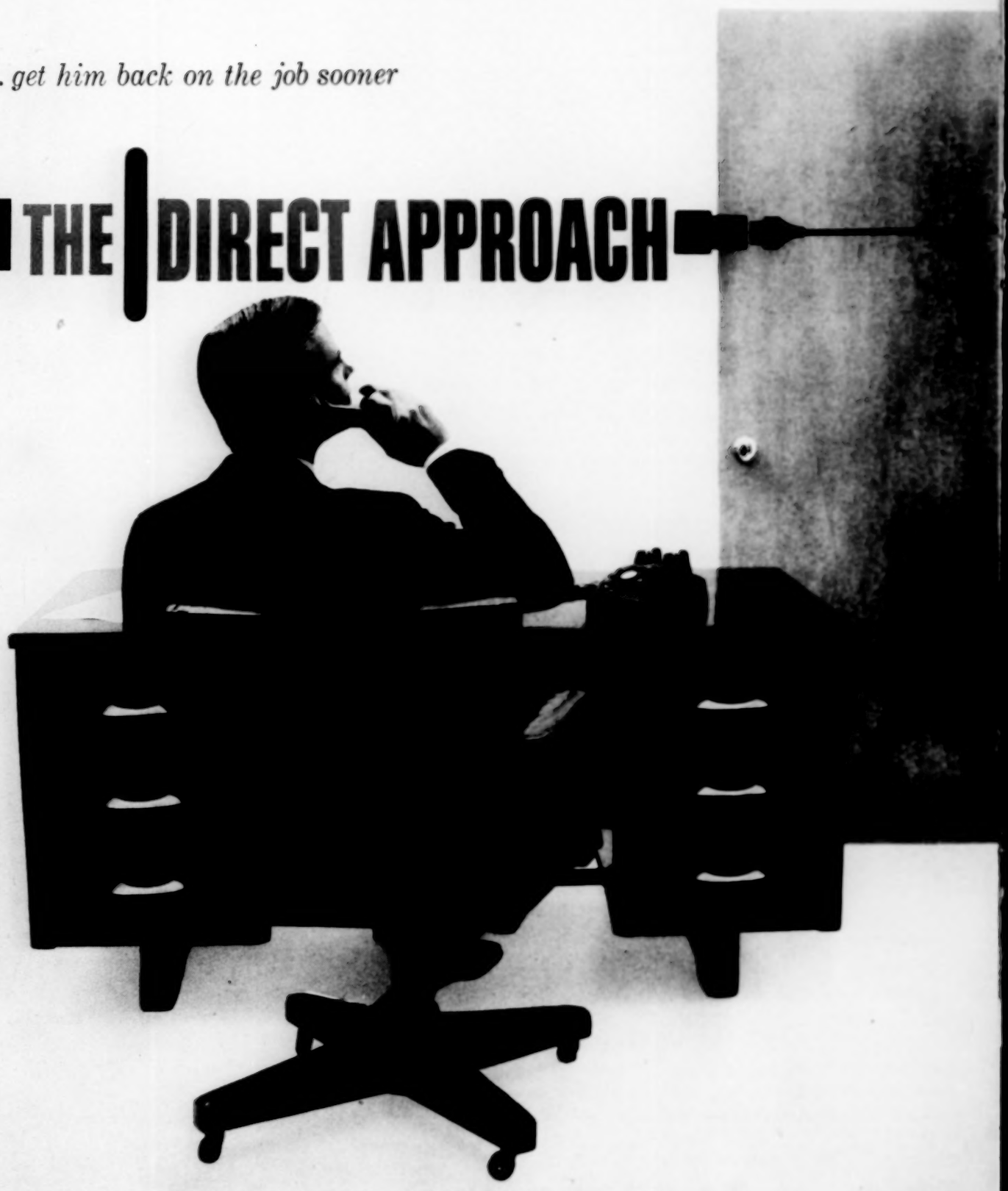

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Literature on Injection DECADRON is available at your request.

DECADRON is a trademark of Merck & Co., Inc.

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Vesprin

Squibb Trifluopromazine Hydrochloride

Doctor...
I have only
two children but
some days
it seems like
twenty-five

controls anxiety and tension in everyday practice

When the patient's normal routine results in anxiety and tension, VESPRIN provides full range action as an effective tranquilizer. And a full range of dosages may be employed depending on the various degrees of emotional disturbance and individual response of the patient. While VESPRIN tranquilizes, it does not produce somnolence, and clinical trials indicate a low order of toxicity and minimal side effects.

Consult Vesprin package insert or PDR for indications, dosage and directions for use. Supply: for oral use—tablets containing 10, 25, and 50 mg. **SQUIBB** Squibb Quality—the Priceless Ingredient

"VESPRIN" IS A SQUIBB TRADEMARK

Upjohn

announces the first progestin since progesterone that will maintain pregnancy even in ovariectomized rats

Ovariectomy of the rat in early pregnancy invariably leads to abortion unless progestin is substituted. Here, rat was ovariectomized on 9th day, and pregnancy maintained on medroxyprogesterone until 21st day, when pups were taken by cesarean section. (From a scientific exhibit, AMA annual meeting, June, 1959).

For the promise of this new compound in your practice, please turn page

The most welcome pain in the world

How much better a pain in the uterus than an ache in the heart! It is pure ecstasy to the habitual aborter, to whom it signifies the imminent fulfillment of her fondest dream.

Only you who have shared her anguish through repeated abortions can fully appreciate her soaring sense of achievement at having finally reached term. Knowing, as you do, the maddening frustration of being powerless to prevent her previous abortions with the ineffective measures that were available at that time, your sense of achievement now parallels hers.

This is the promise of Provera—a new, oral progestin developed by Upjohn research. Because it represents the first clinically-significant improvement on progesterone, we believe Provera constitutes the most important advance in the treatment of idiopathic recurrent abortion in 30 years.

It is the only compound, other than progesterone, that will maintain pregnancy in ovariectomized rats. And it is approximately 40 times as potent as progesterone, which makes oral therapy of habitual abortion practical for the first time.

And Provera exerts no significant androgenic or estrogenic effect whatever—which makes it a "purer" progestational agent than progesterone itself.

We invite you to select the most critical 60 days of pregnancy as your test. Use Provera (10 to 20 mg./day) to carry your next habitual aborter through the dangerous period during which the production of endogenous progesterone shifts from the corpus luteum to the placenta (usually in the third and fourth months). The cost to your patient will be a pleasant surprise.

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when the
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in the
clotting chain is
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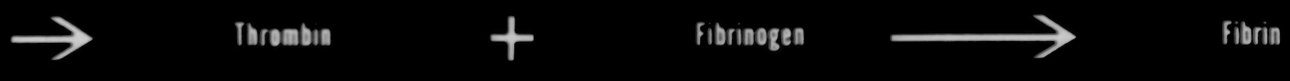
Thromboplastin + Prothrombin + Calcium —

the preferred antidote is

Mep



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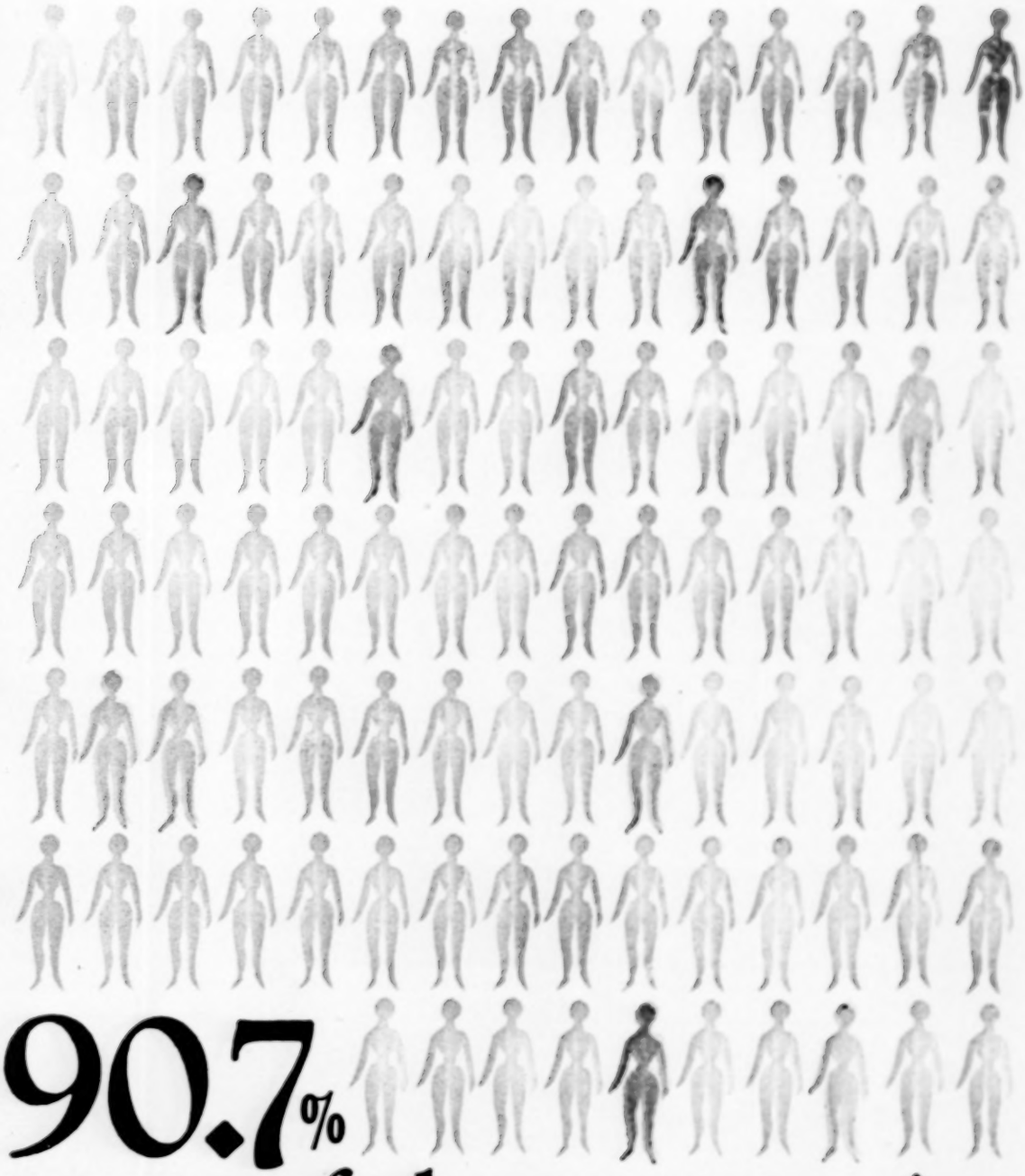

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*Murphy, H. S., *et al.*, Scientific Exhibit, A.M.A., Dec. 1-4, 1953, Dallas, Texas

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Benadryl® hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	80 mg.
Ammonium chloride	12 gr.
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Alcohol	5%

supplied: BENYLIN EXPECTORANT is available in 16-ounce and 1-gallon bottles.

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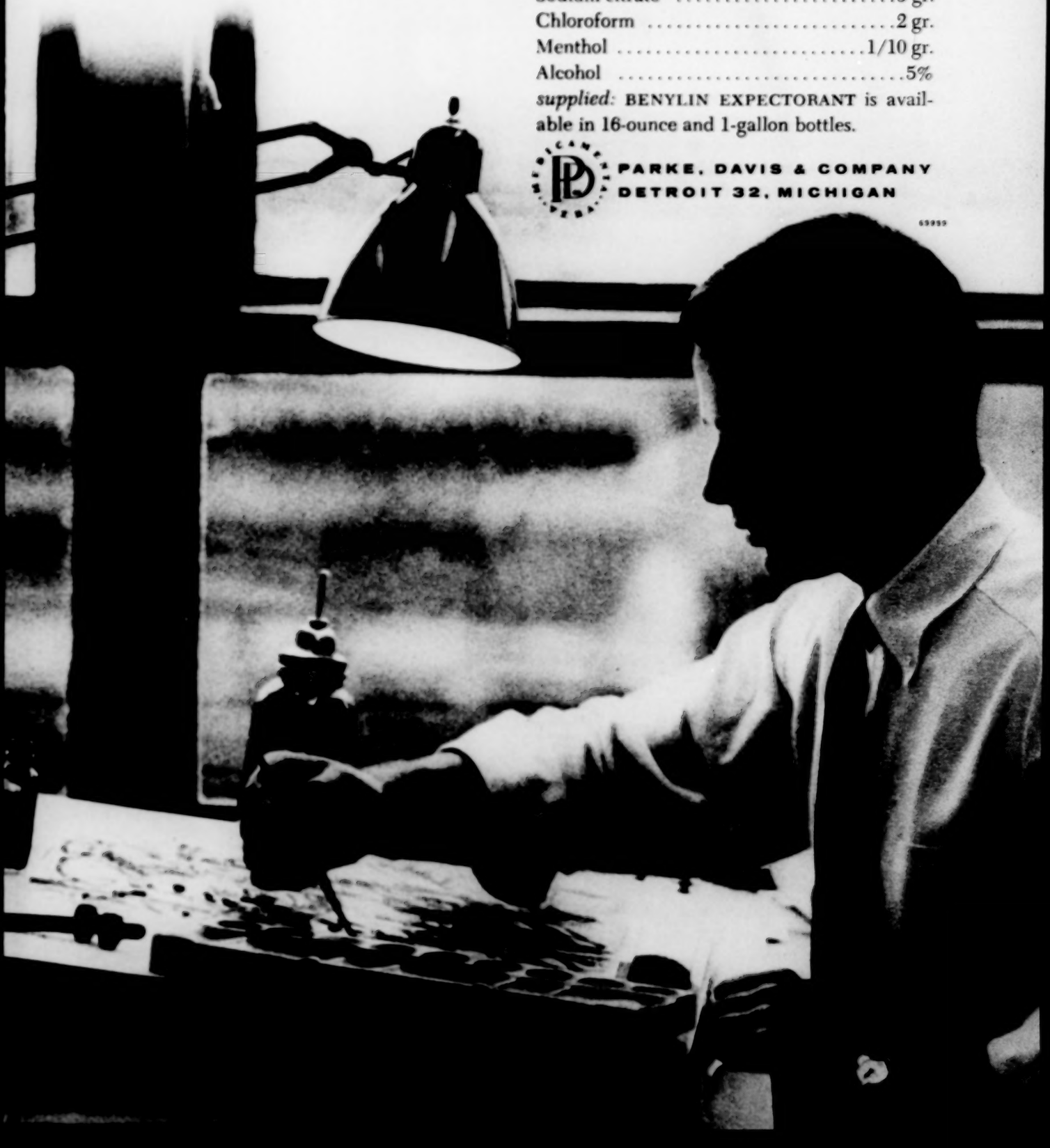

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In diabetic acidosis, can it be assumed that the greater the biochemical derangement the more severely will consciousness be impaired?

No. The state of consciousness does not parallel the metabolic disturbance but it does affect the prognosis.

Source: Green, H. L., and Whitehouse, F. W.: J. Michigan M. Soc. *57*:1410, 1958.

diabetics most vulnerable to acidosis...

- labile diabetics • newly diagnosed diabetics
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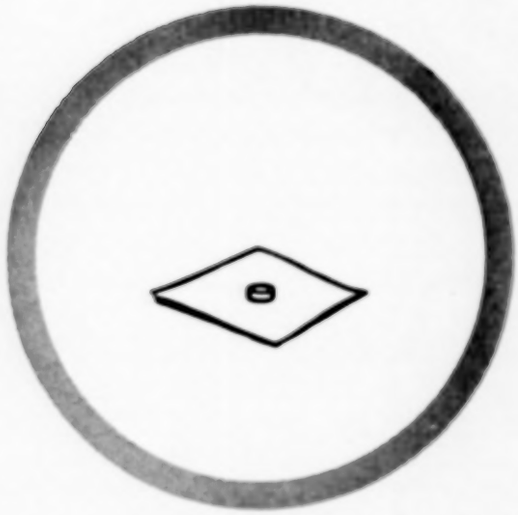

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Fear, agitation, and resistance often hinder medical diagnosis and treatment.

SPARINE alleviates agitation, overcomes resistance, placates fears.

In addition to calming the patient, SPARINE controls other interfering symptoms: nausea, vomiting, and hiccups.

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COMPARE THE DATA ON ENARAX . . . the new combination of an **inherently** long-acting anticholinergic (oxyphencyclimine) and Atarax, the non-secretory tranquilizer. Note the effectiveness of oxyphencyclimine:

OBSERVE THE OXYPHENCYCLIMINE REPORTS . . .

McHardy: "[Oxyphencyclimine] has proved to be an excellent sustained-action anticholinergic in our study of this agent over a period of eighteen months."[1]

Kemp: ". . . for the majority of patients, one tablet every 12 hours provided adequate control. This characteristic long action . . . may constitute an advantage of this drug as compared to coated 'long-acting' preparations of other compounds."[2]

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LOOK AT THE RESULTS WITH ENARAX*[1,2]

Does the medication you now prescribe assure you of all these benefits? If not, why not put your next patient with peptic ulcer or G.I. dysfunction on therapy that **does.**

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(oxyphencyclimine plus ATARAX®)

A SENTRY FOR THE G.I. TRACT

PROVIDE CONTINUOUS CONTROL OF ACID SECRETION?

"Prolonged periods of achlorhydria" after 10 mg. oxyphencyclimine q. 12 h.[1]

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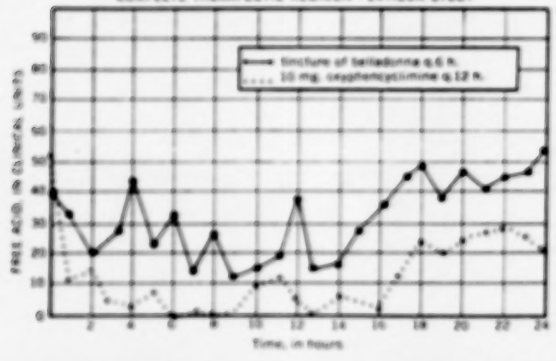

Clinical Diagnosis: Peptic Ulcer – Gastritis – Gastroenteritis – Colitis – Functional Bowel Syndrome – Duodenitis – Hiatus Hernia (symptomatic) – Irritable Bowel Syndrome – Pylorospasm – Cardiospasm – Biliary Tract Dysfunctions – and Dysmenorrhea.

Clinical Results: Effective in over 92% of cases.

As for Safety: "Side reactions were uncommon, usually no more than dryness of the mouth. . . ."[4]

Each ENARAX tablet contains:

Oxyphencyclimine HCl ..... 10 mg.
Hydroxyzine (ATARAX®) ..... 25 mg.

Dosage: One-half to one tablet twice daily – preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and with ophthalmological supervision only in glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.

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- No sympathomimetic stimulation
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Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydroalcoholic vehicle (alcohol 20%).

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For 24 hour control: For adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, 1st 6 doses 0.3 cc.—then 0.2 cc. (per lb. of body weight) as above.

1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

REFER TO PDR PAGE 812

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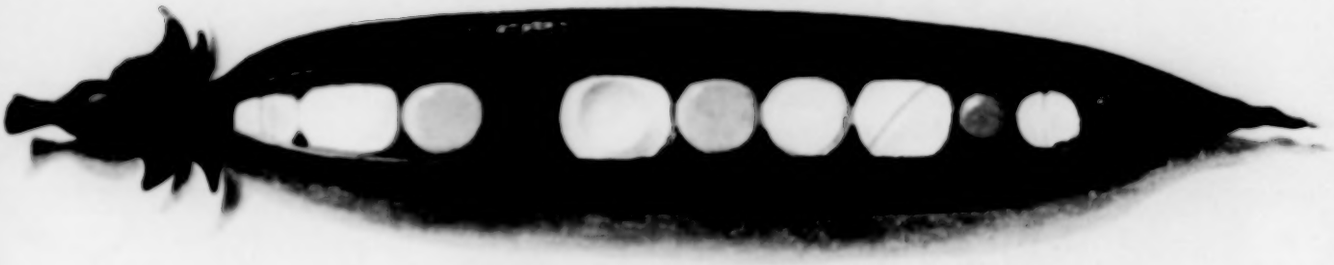

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THIORIDAZINE HCl

provides highly effective tranquilization, relieves anxiety, tension, nervousness,

but is virtually free of such toxic effects as

jaundice
Parkinsonism
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greater specificity of tranquilizing action results in fewer side effects

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such "diffuse" effects as anti-emetic action.

Mellaril

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specific, effective tranquilizer

"Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines....This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 100 mg.

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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

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Decongestant / Antihistamine

THE POTENTIATED DECONGESTANT

provides symptomatic relief of nasal congestion and rhinorrhea of allergic or infectious origin Many patients whose symptoms are inadequately controlled by decongestants or antihistamines alone respond promptly and favorably to 'ACTIFED'.

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'Actidil'® brand Triprolidine Hydrochloride	2.5 mg.	1.25 mg.
'Sudafed'® brand Pseudoephedrine Hydrochloride	60 mg.	30 mg.

safe and effective for patients of all ages suffering from upper respiratory tract congestion

DOSAGE

	TABLETS	SYRUP (5 cc. tsp.)	
Adults and older children	1	2	three times daily
Children 4 months to 6 years of age	½	1	
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PROBENECID
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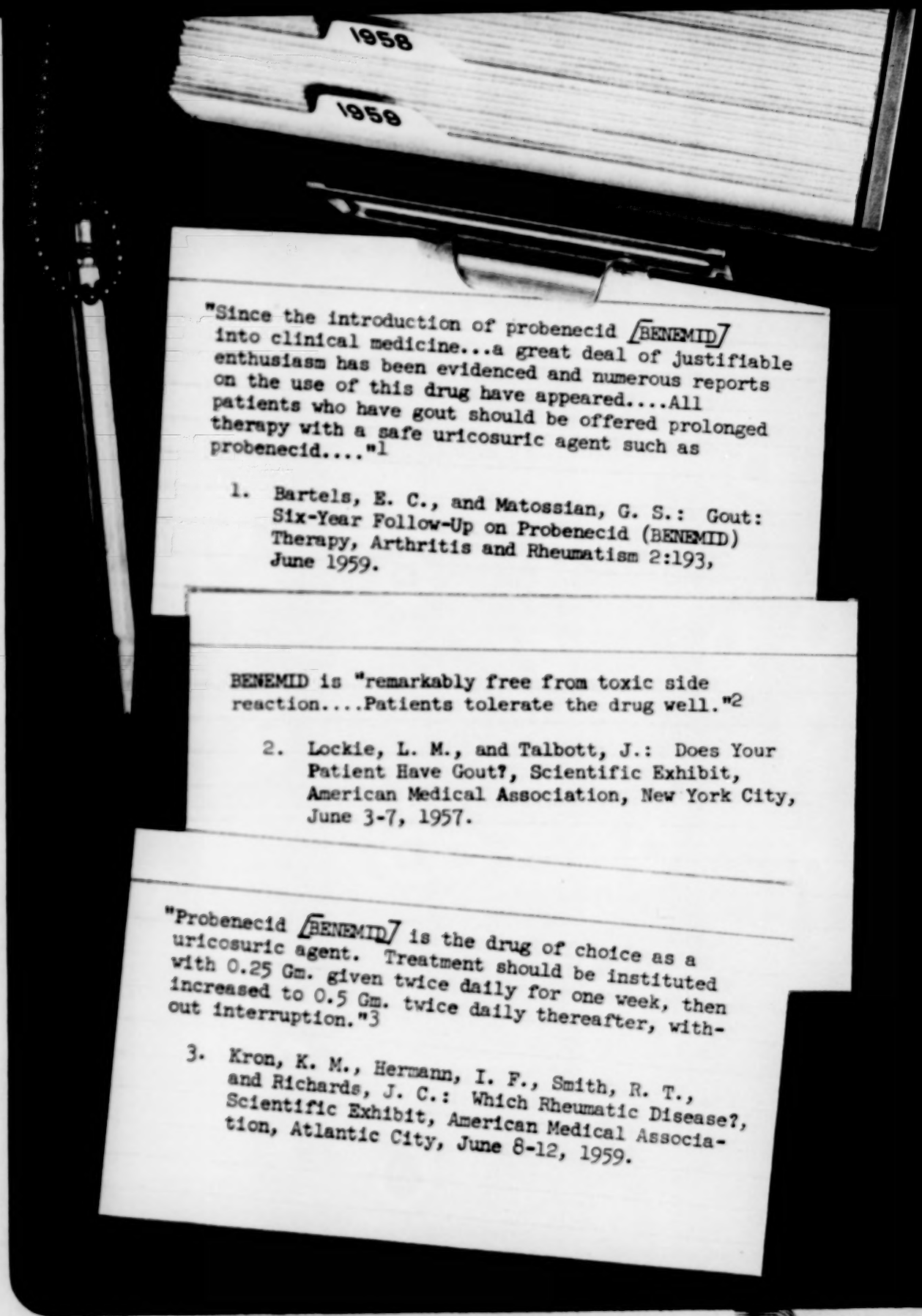
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"Since the introduction of probenecid [BENEMID] into clinical medicine...a great deal of justifiable enthusiasm has been evidenced and numerous reports on the use of this drug have appeared....All patients who have gout should be offered prolonged therapy with a safe uricosuric agent such as probenecid...."1
1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.
BENEMID is "remarkably free from toxic side reaction....Patients tolerate the drug well."2
2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.
"Probenecid [BENEMID] is the drug of choice as a uricosuric agent. Treatment should be instituted with 0.25 Gm. given twice daily for one week, then increased to 0.5 Gm. twice daily thereafter, without interruption."3
3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

Supply: 0.5 Gm. tablets, bottles of 100 and 1000.

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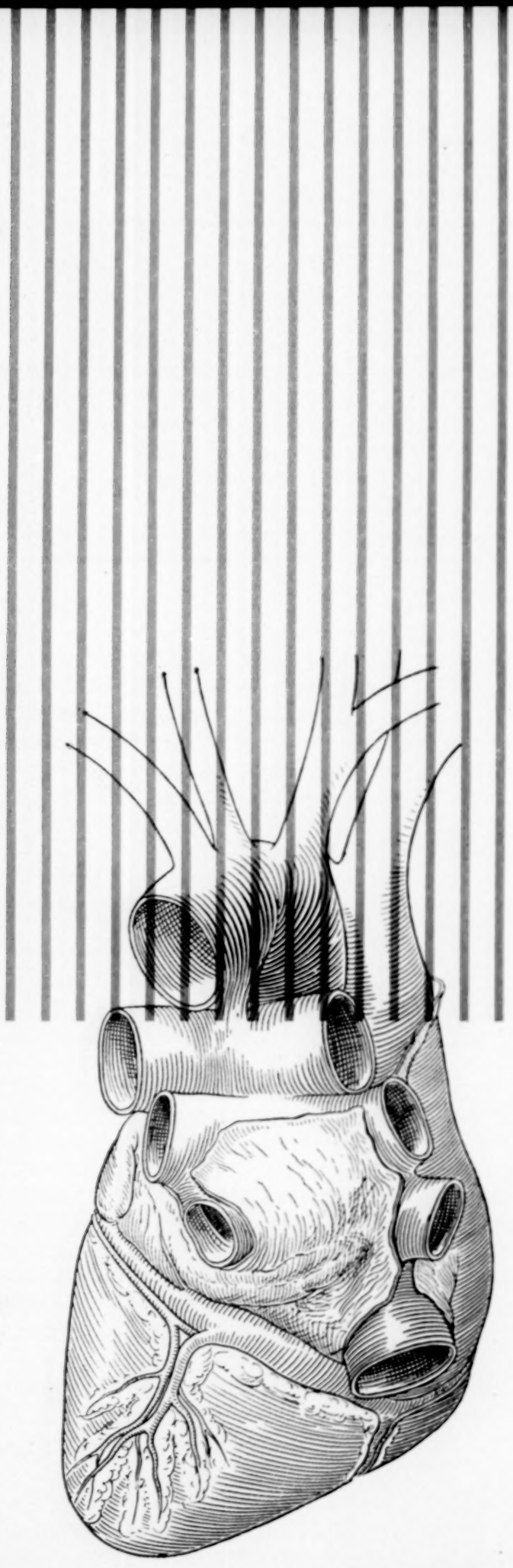

Now, a single agent, important clinical

for total management of angina pectoris

Marplan prevents pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.[1-3] To date, Marplan prophylaxis has been evaluated in over 300 angina patients. The response rate was 76 per cent with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1] One study reported "excellent effects with relatively small doses" and "greater relief than [with] any other compound in our experience."[3]

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris and, while it frequently abolishes anginal pain, Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.

with two distinct primary effects, for two indications

Marplan

a happy balance of potency/safety

A broad clinical research program continues to define the full range of Marplan's clinical applicability. However, already some 300 research clinicians have evaluated Marplan in more than 4000 patients in two primary diagnostic categories—*angina pectoris and depression.*

Marplan has been shown to be considerably more active than other amine oxidase regulators. While clinically such increase in potency has heretofore been associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of the side reactions of the hydrazines. Moreover, throughout the extensive clinical investigations, no liver damage has been reported. Marplan is an amine oxidase regulator, however, and like all of these agents, it is contraindicated in the presence of liver or kidney disease.

Consult complete literature and dosage instructions, available on request, before prescribing.

Bibliography: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. I. Kimbell, paper read at Co-operative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959.

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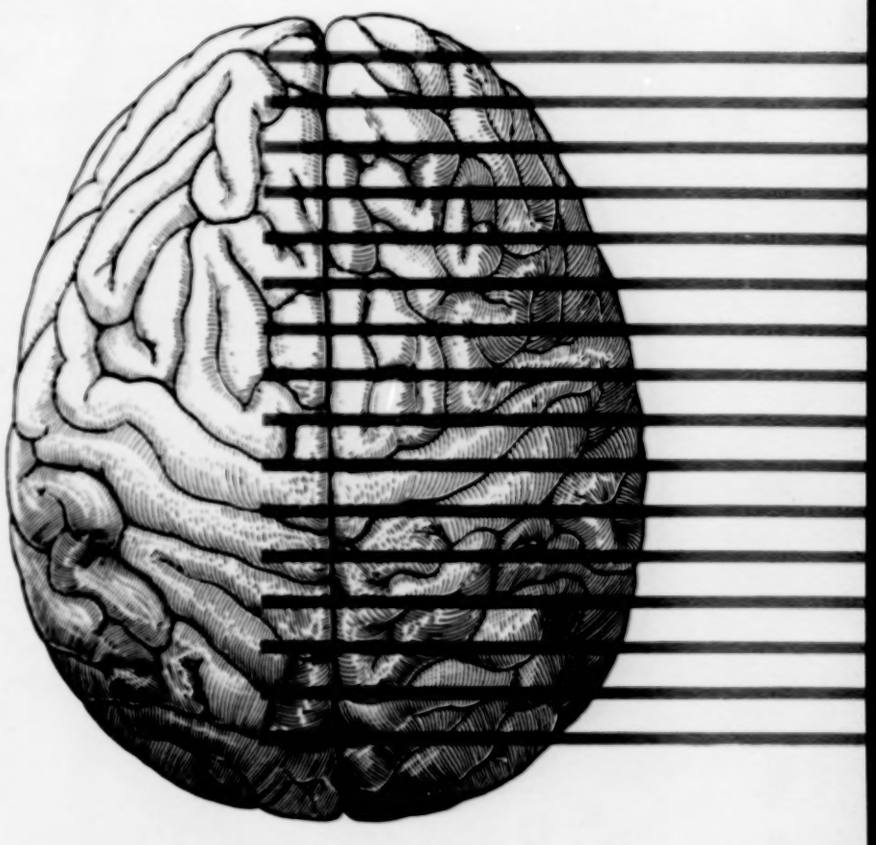
to lift depression

The value of Marplan in depression: Marplan is indicated in the broad range of emotional and psychiatric disorders with associated symptoms of depression, withdrawal or regression. To date, Marplan has been fully evaluated in more than 3700 patients with depression. The majority (67 per cent) showed significant improvement[1]: "Depression of mood and somatic preoccupation were less pronounced, concentration improved, irritability lessened, and the patients appeared to be more relaxed."[4]

Marplan in rheumatoid arthritis: Marplan has also been found to be valuable adjunctive therapy in the management of rheumatoid arthritis and other chronic debilitating disorders with associated depressed psychomotor activity.



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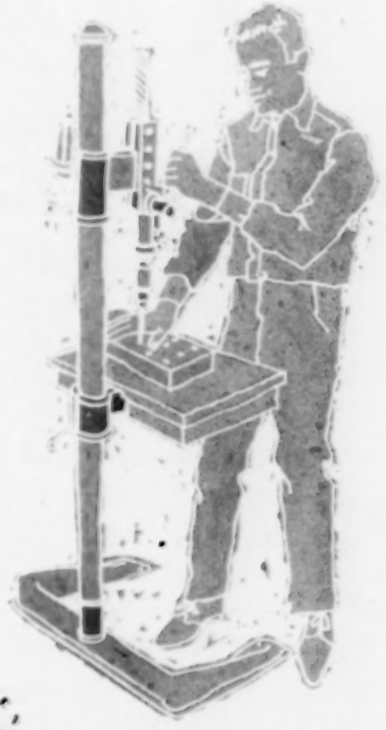

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as white, coated, 350 mg. tablets, bottles of 50. Also available for pediatric use: 250 mg. orange capsules, bottles of 50.

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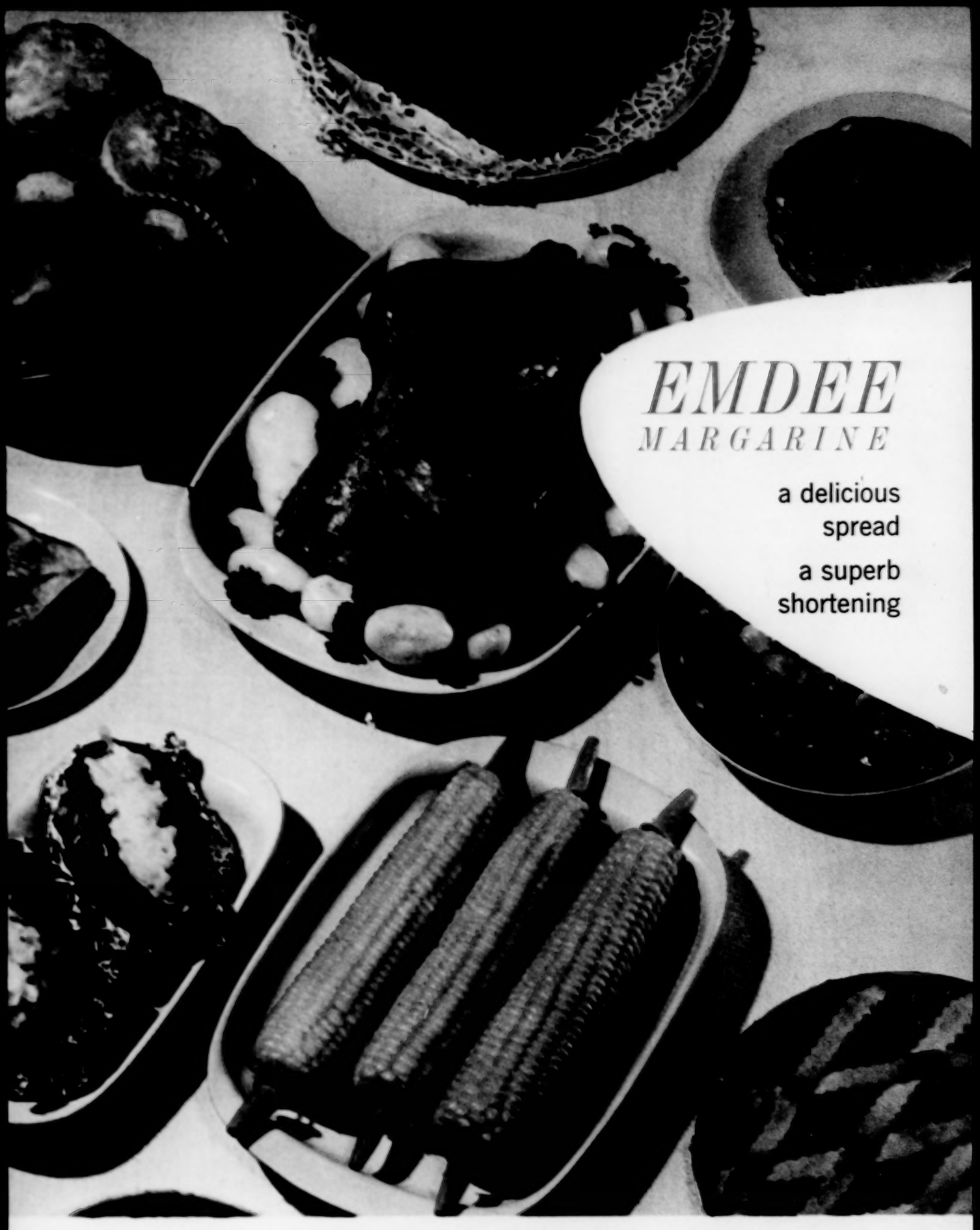

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Eighty per cent of Emdee Margarine's fat content is pure corn oil, whose natural content of polyunsaturated fatty acids has not been destroyed by hydrogenation.* Approximately 45% of its fat content is linoleic acid, an important substance in the control of blood cholesterol levels.

When a patient's intake of saturated fats should be reduced, he and his family will welcome Emdee Margarine. It restores natural flavor to a cholesterol-reducing diet and eliminates the chore of preparing special dishes for one member of the family.

On bread, toast and crackers Emdee Margarine has the same taste as other fine spreads, and a firm, smooth texture. It brings back the familiar flavor to baked potatoes, vegetables and popcorn. It can be used for braising, baking, roasting and sautéing, and in white sauces and frostings. It has won praise from Home Economics experts, who found that Emdee Margarine is a high-quality shortening.

Packaged in one-pound cans to protect its fresh taste and firm texture, Emdee Margarine is *available only in pharmacies.*

References: 1. Terman, L. A.: Dietary management of hypercholesterolemia, Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. T.; Gardier, R. W., and Ralston, J. D.: A new dietary management of hypercholesterolemia, J.A.M.A., in press. 3. Vail, Gladys E.: Cooking with fats high in polyunsaturated fatty acids, J. Am. Dietet. A. *35*:119 (Feb.) 1959.

Reprints of these articles on Emdee Margarine are available on request.

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anxiety pushing it up?

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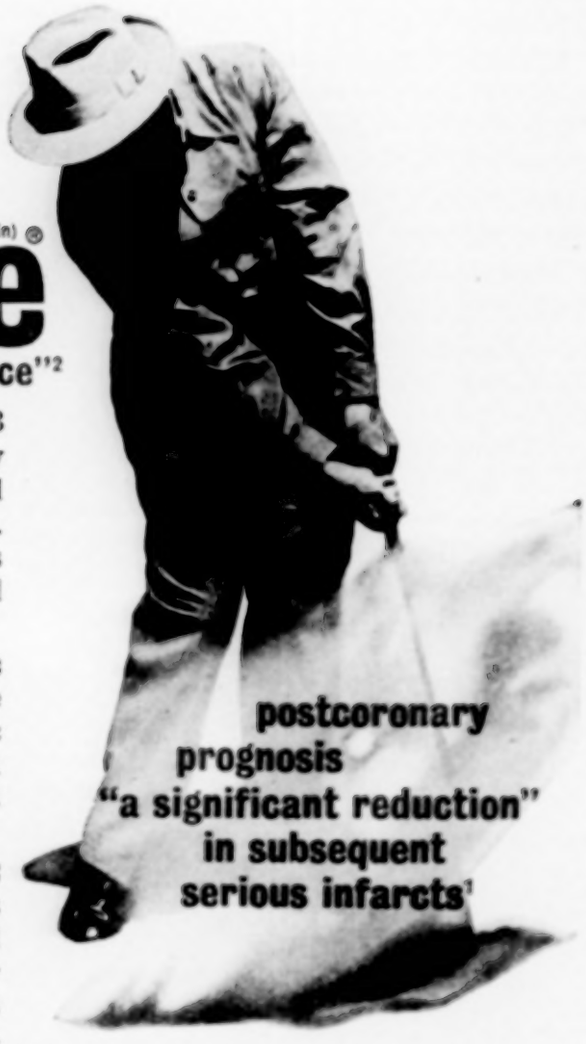

When DANILONE was administered to 33 postmyocardial infarct patients, only two thromboembolic episodes occurred in two patients in 565 patient-months. Five such episodes in 50 patient-months occurred in four patients who had stopped taking anticoagulants.[3]

"twice as fast in reaching therapeutic levels"[4] In 117 patients, the average time DANILONE required to attain therapeutic levels was less than 36 hours.[4] With bishydroxycoumarin, two to four days are required for equal effect.[5]

"a greater degree of control"[6] DANILONE held prothrombin activity in 200 patients to between 5 and 10 per cent of normal "with greater facility" than in another series where bishydroxycoumarin was used.[6] Generally, most satisfactory control can be obtained by dividing the dosage schedule into two 12-hour intervals.[3,6]

"a reputation for safety"[7] DANILONE, unlike the coumarin derivatives, has a short recovery period and no cumulative action.[5,8,9] As a result, DANILONE "...can be administered with reasonable safety in the presence of many conditions which would contraindicate the use of Dicoumarol."[6]

"a lack of toxic reactions"[3] Because of its extremely low incidence of toxicity,[2,4,9] and "...the apparent safety factor of a wide spread between therapeutic and toxic dose, it is felt that phenyldanedione [phenindione] is the anticoagulant drug of choice."[2]

"inexpensive"[5] DANILONE is the least expensive anticoagulant available today. Maintenance cost is as little as three cents a day. In addition, its stability of effect permits fewer prothrombin-time tests,[9] saving the patient additional costs.

Samples and literature available on request.

SUPPLIED: 50 mg. scored tablets. Bottles of 100 and 1,000.

References: 1. Pickering, G., et al.: Brit. M. J. 1:803 (Mar. 28) 1959. 2. McCabe, E. S., and Fittipoldi, J., Jr.: Am. Pract. & Digest Treat. 4:765, 1953. 3. Drinan, F. W., et al.: Am. Heart J. 53:284, 1957. 4. Harper, B. F., and Johnson, R.: J.M.A. Georgia 45:149, 1956. 5. Wood, J. E.; Beckwith, J. R., and Camp, J. L., III: J.A.M.A. 159:635 (Oct. 15) 1955. 6. Sise, H. S.; Maloney, W. C., and Guttas, C. G.: Am. Heart J. 53:132, 1957. 7. Newcomb, T. F.: New England J. Med. 260:545 (Mar. 12) 1959. 8. O'Connor, W. R.; Thompson, C. E., and Baker, L. A.: Quart. Bull. Northwestern Univ. M. School 26:193 (Fall) 1952. 9. Toohey, M.: Brit. M. J. 1:650 (Mar. 21) 1953.

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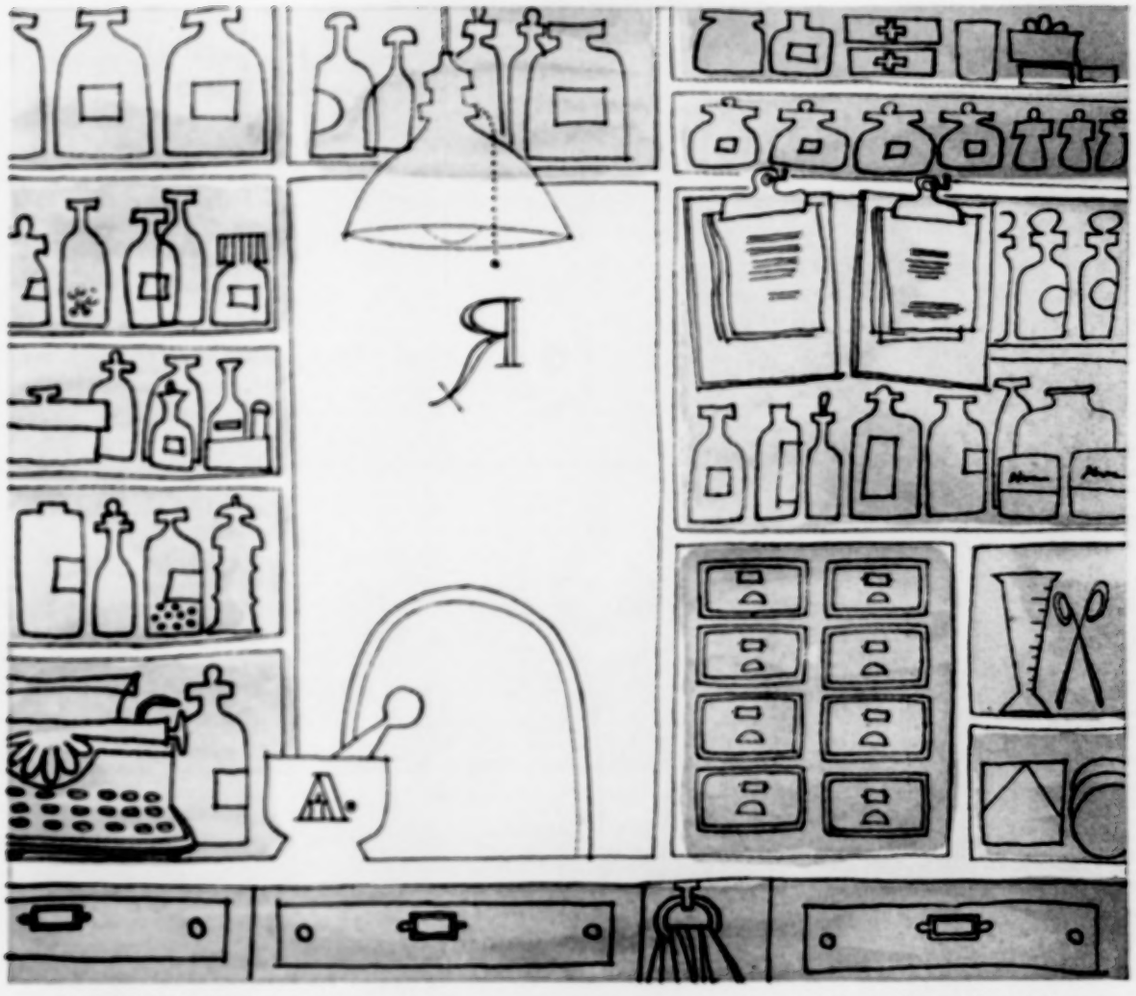

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Relieves interval pain[2,4]—reduces joint swelling[3]—improves mobility.[2]

References:
1. Yu, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. *1*:552, 1958. 2. Gutman, A. B., and Yu, T. F.: Bull. N. Y. Acad. Med. *34*:287, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. *17*:326, 1958. 4. Ogryzlo, M. A., and Harrison, J.: Ann. Rheumat. Dis. *16*:425, 1957.

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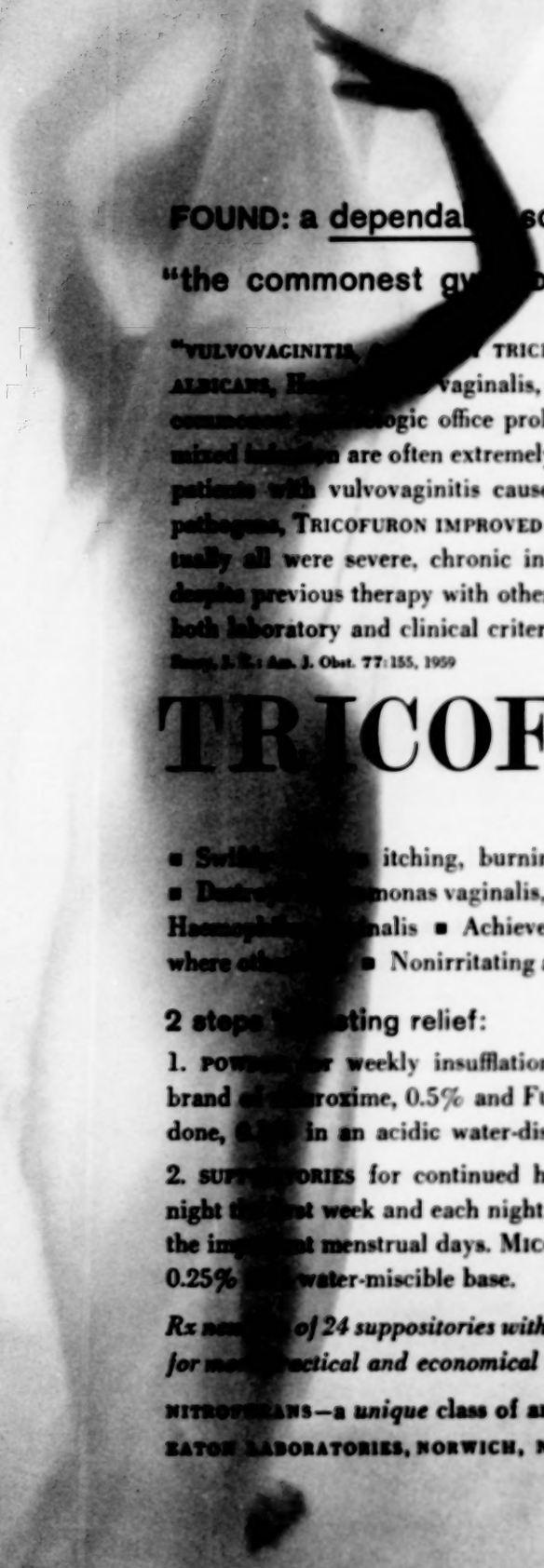

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Burg, J. R.: Am. J. Obst. 77:155, 1959

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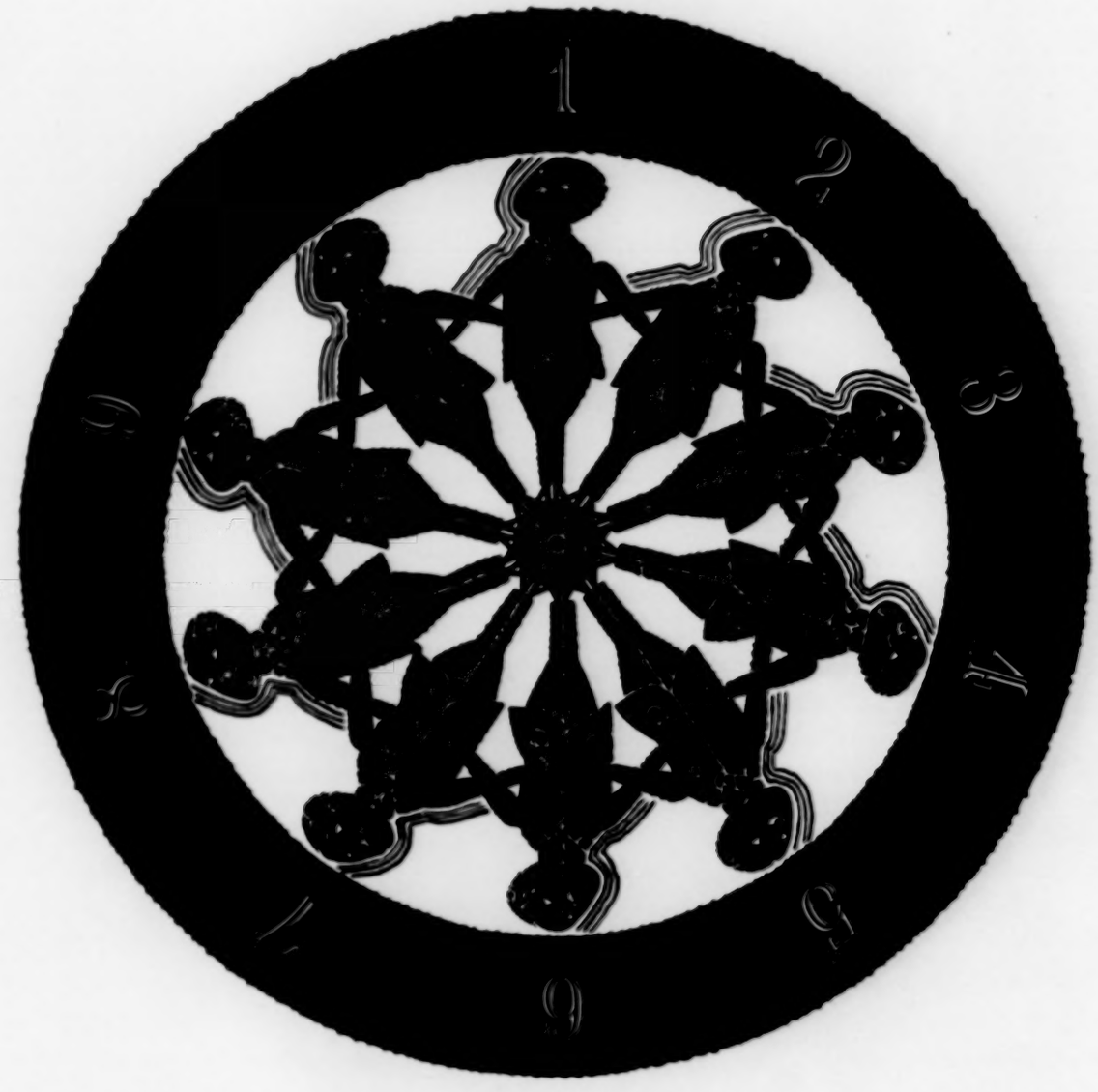

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Prescribe one ANTIVERT tablet (12.5 mg. meclizine; 50 mg. nicotinic acid) before each meal for relief of Meniere's syndrome, arteriosclerotic vertigo, labyrinthitis and vertigo of nonspecific origin.

Supplied: In bottles of 100 blue-and-white scored tablets. Prescription only.

References: 1. Menger, H. C.: Clin. Med. 4:313 (Mar.) 1957. 2. Seal, J. C.: Eye Ear Nose & Throat Month. 38:738 (Sept.) 1959.

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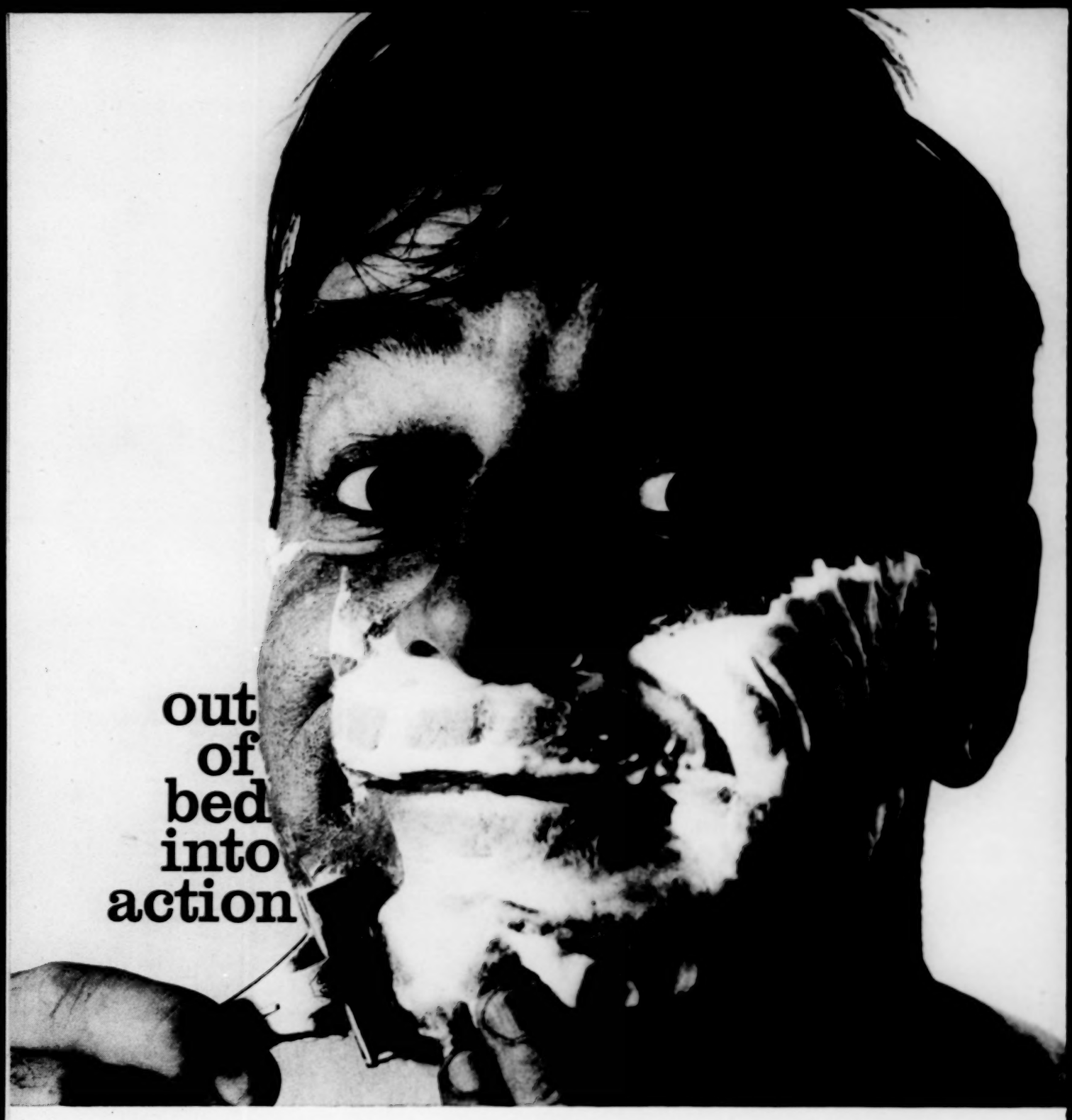

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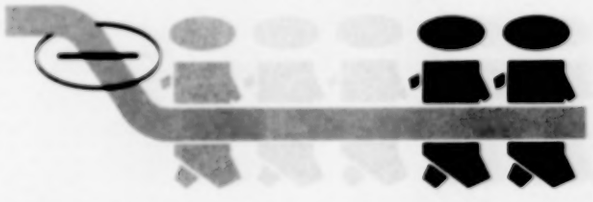

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Jackson, D., and Oakley, W.: Lancet 2:752, 1959

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How to Prescribe **PERMITIL:** The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

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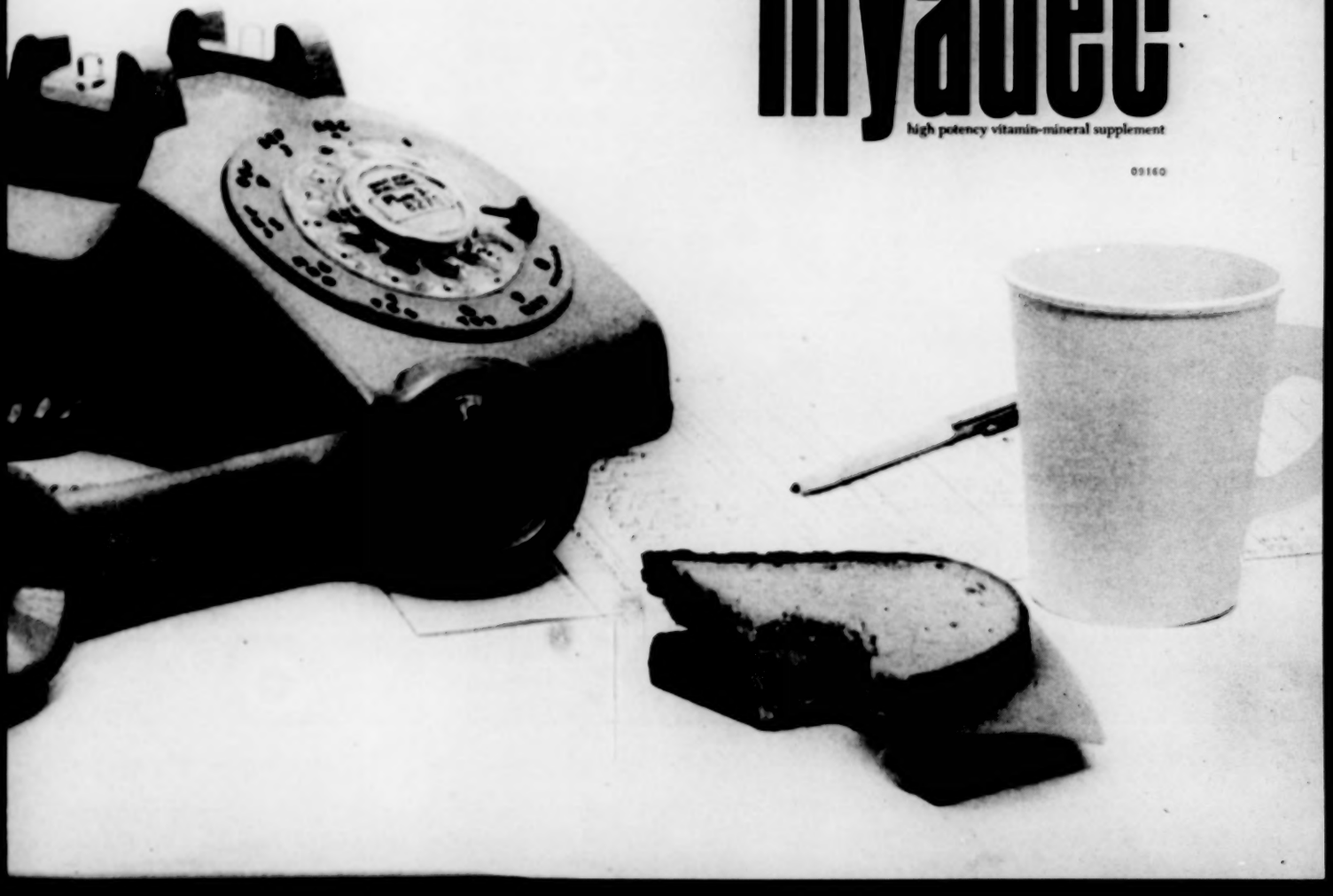


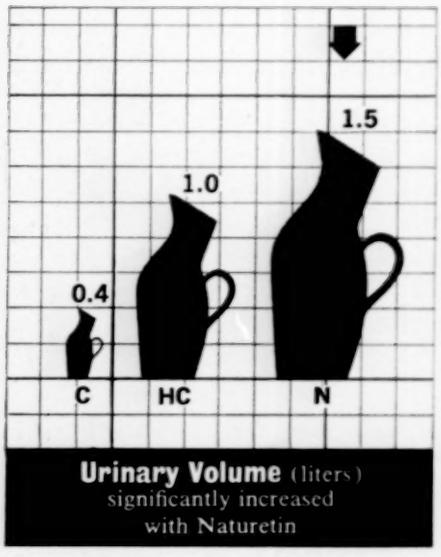
more closely approaches the ideal diuretic

Naturētin

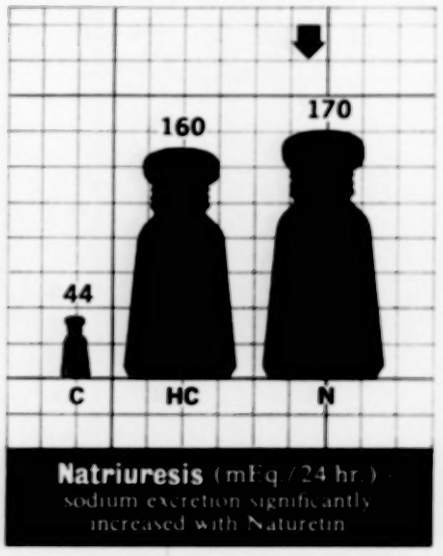
Squibb Benzydroflumethiazide

"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." ***Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.***

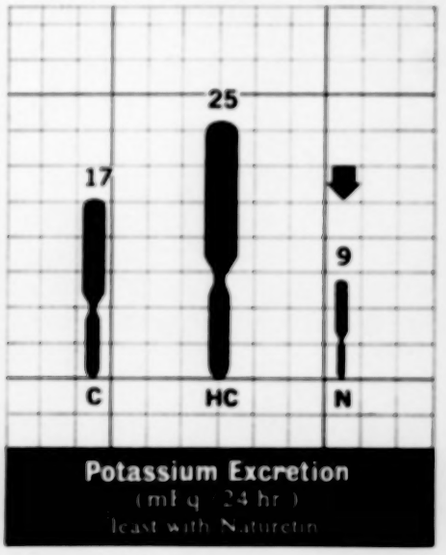
Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



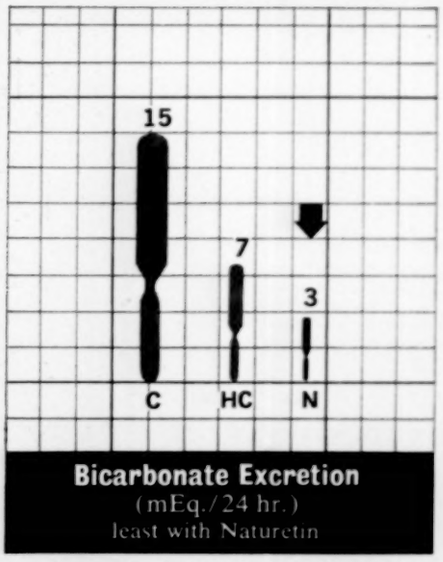
Urinary Volume (liters)
significantly increased
with Naturetin



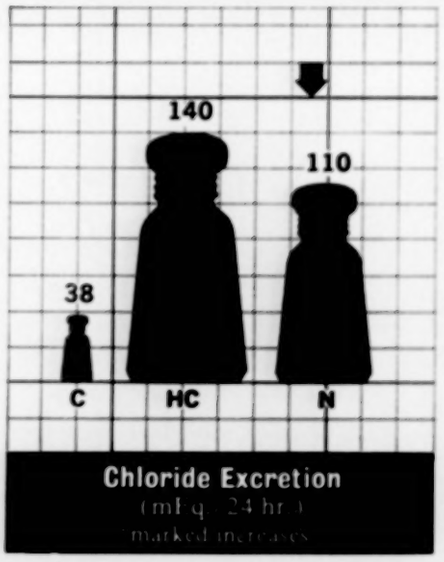
Natriuresis (mEq./24 hr.)
sodium excretion significantly
increased with Naturetin



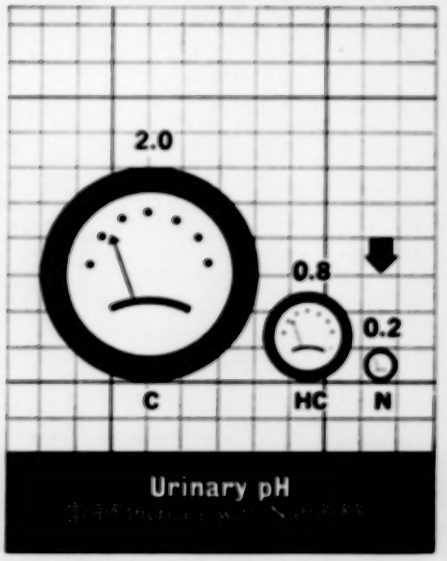
Potassium Excretion
(mEq./24 hr.)
least with Naturetin



Bicarbonate Excretion
(mEq./24 hr.)
least with Naturetin



Chloride Excretion
(mEq./24 hr.)
marked increases



Urinary pH

Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage – more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturetin – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturetin – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturetin – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

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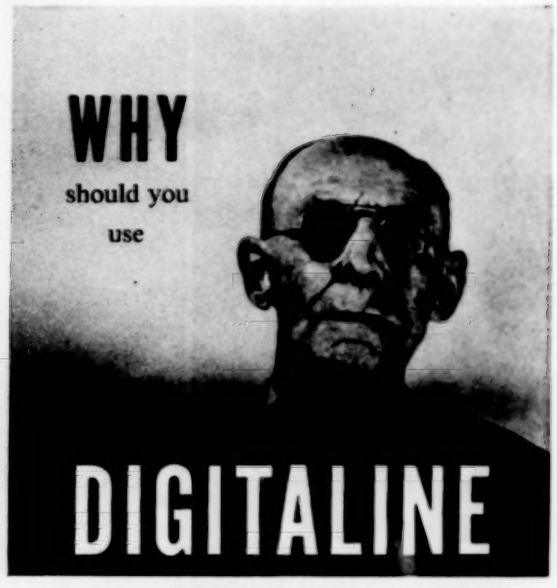

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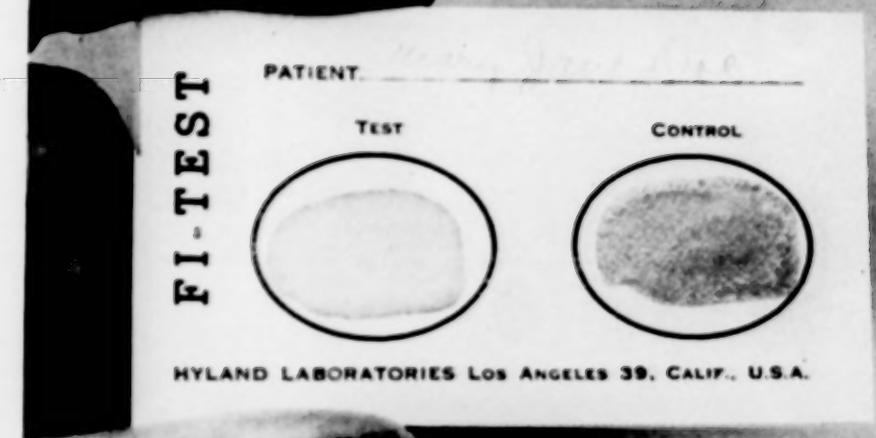

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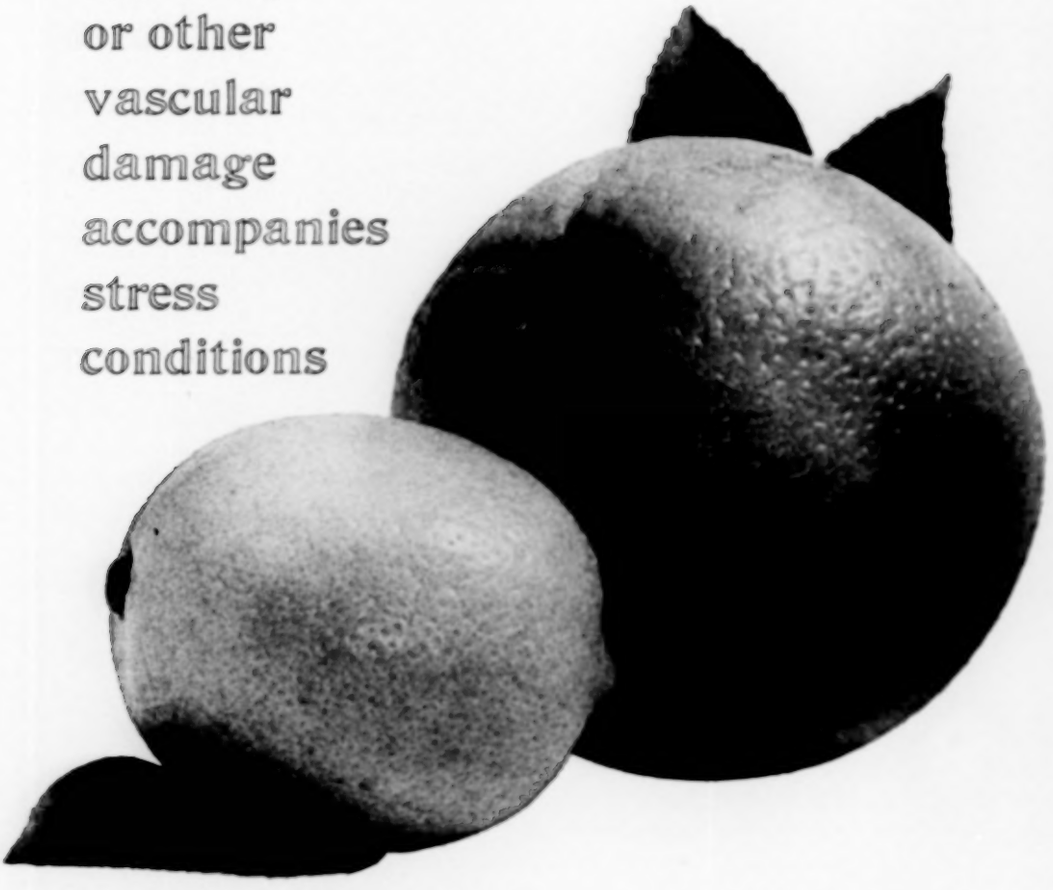

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Incidence of impaired capillary function is more frequent than previously recognized. Many publications indicate the frequency of increased capillary weakness ranges from 16% to as high as 80% of patients examined (1-4).

Reports show older people have a high incidence of capillary fragility (6). In a group of 111 patients, capillary weakness was noted to be greatest in the fifth and sixth decades (5).

Hypertensives (7, 8, 9) and those with chronic diseases such as arteriosclerosis, diabetes and rheumatoid arthritis, have shown varying degrees of capillary involvement. Hemorrhagic conditions of the brain and heart have shown localized injury in the capillary (10, 11).

Capillary fragility has been shown to be associated with many bacterial, viral and inflammatory diseases (12-23).

Various bioflavonoid materials have been evaluated for their effect upon the capillary. Degree of fragility has been determined by numerous procedures (24-30).

The therapeutic rationale of combining *Hesperidin* or other *citrus bioflavonoids* with ascorbic acid or other therapeutic agents is based on the premise that capillary weakness may be a contributing factor to the disease state and that capillary integrity should be maintained. *Citrus bioflavonoids* in conjunction with ascorbic acid appear to enhance the efficacy of other therapy, and help control such factors as infection, stress and nutritional deficiency even in cases not showing capillary weakness.

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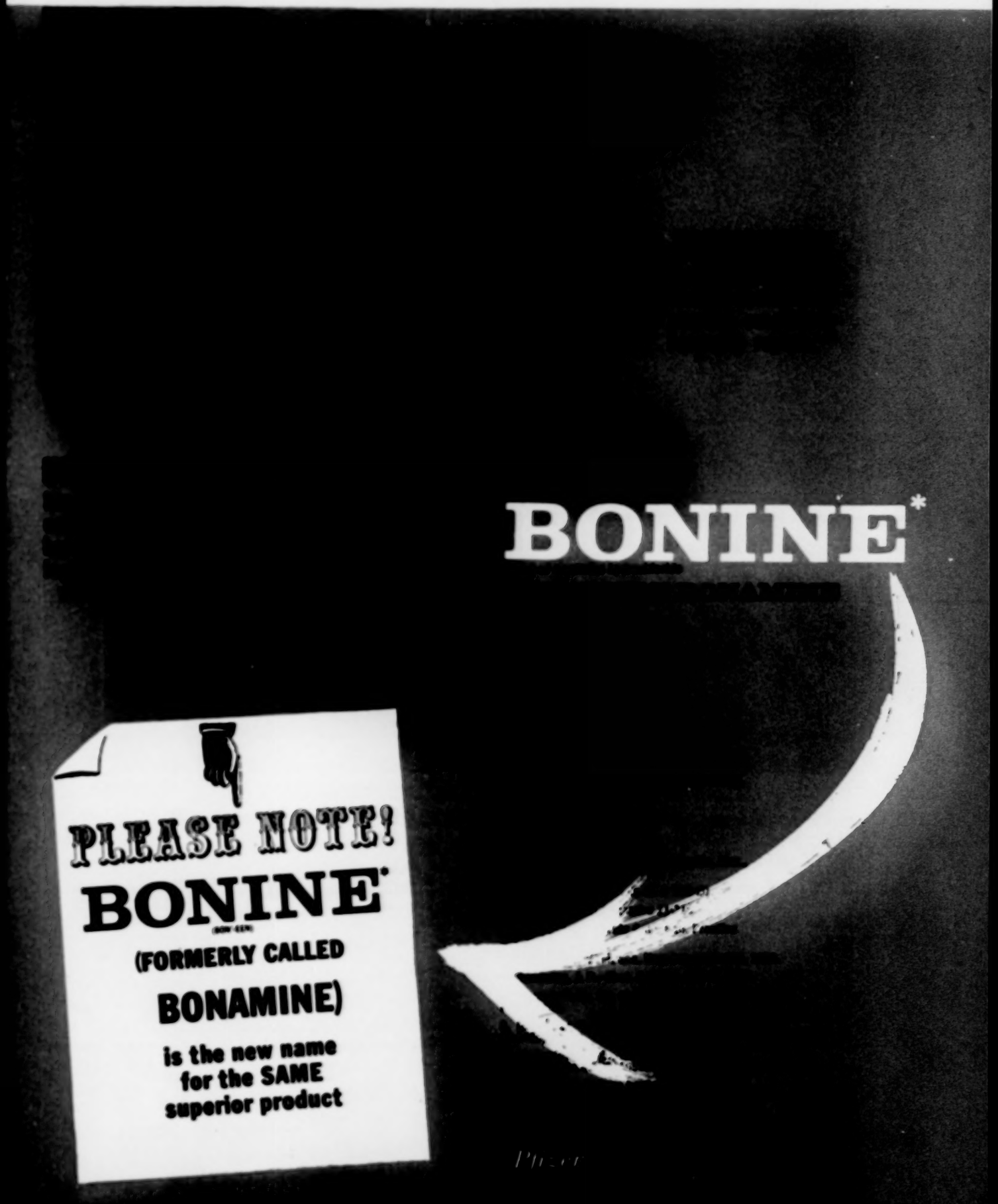

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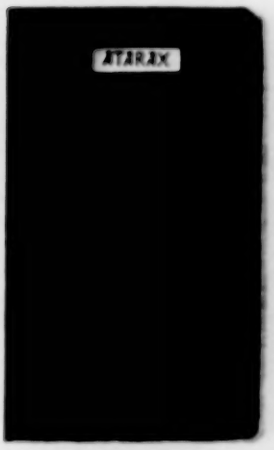

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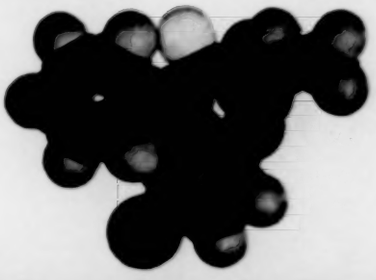

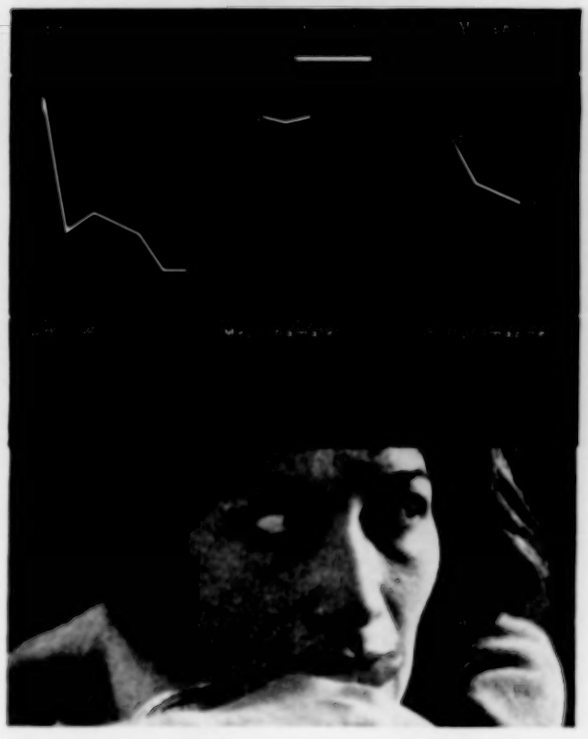

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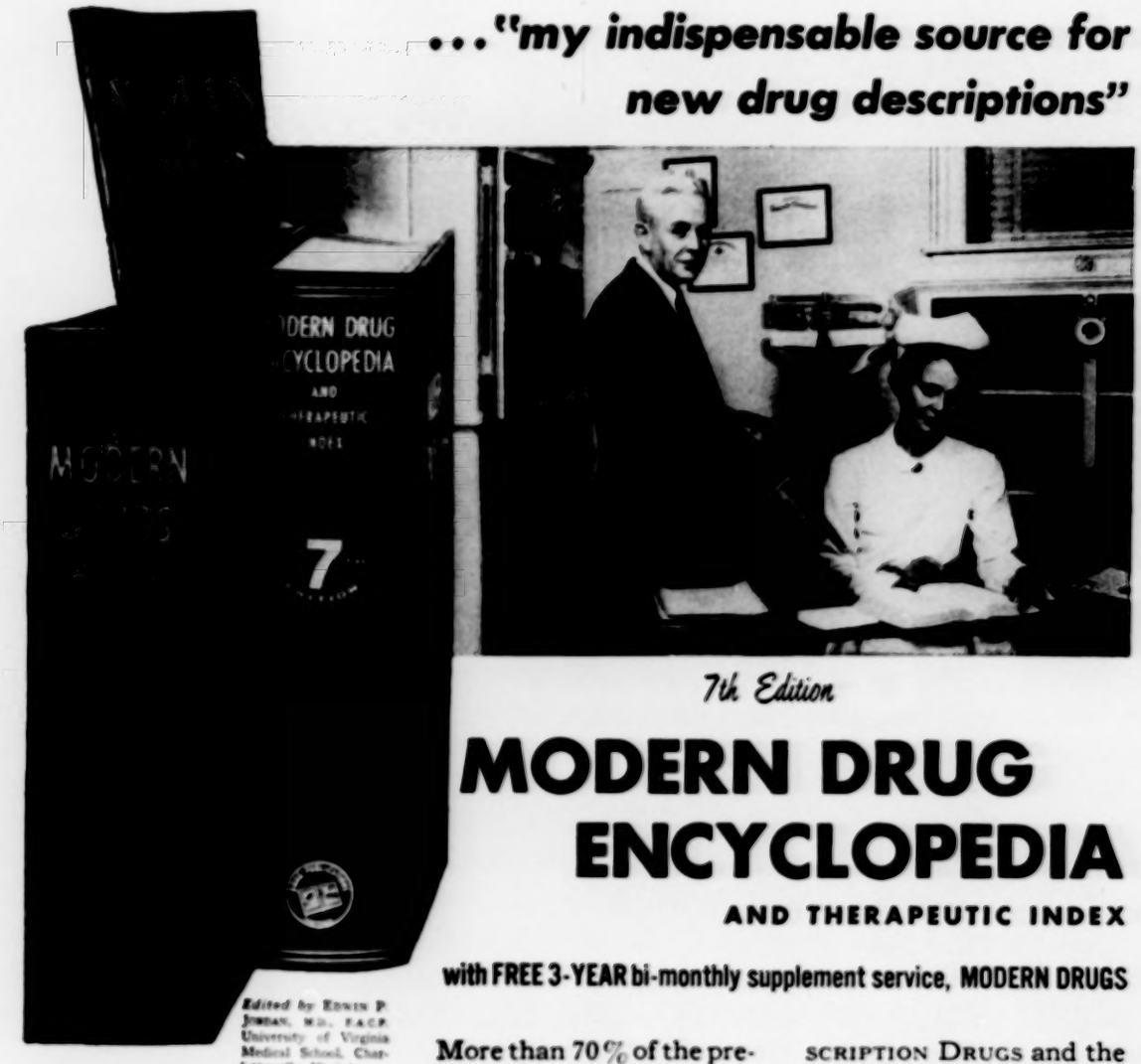

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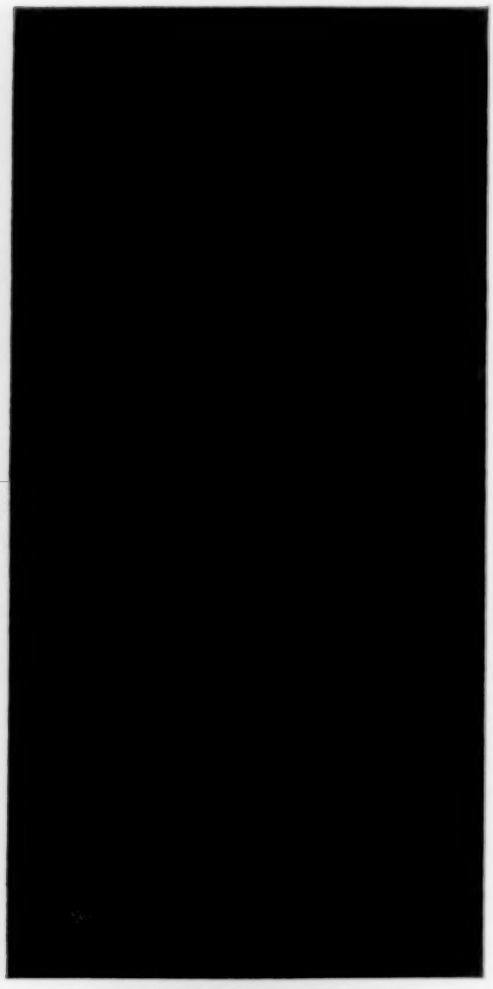

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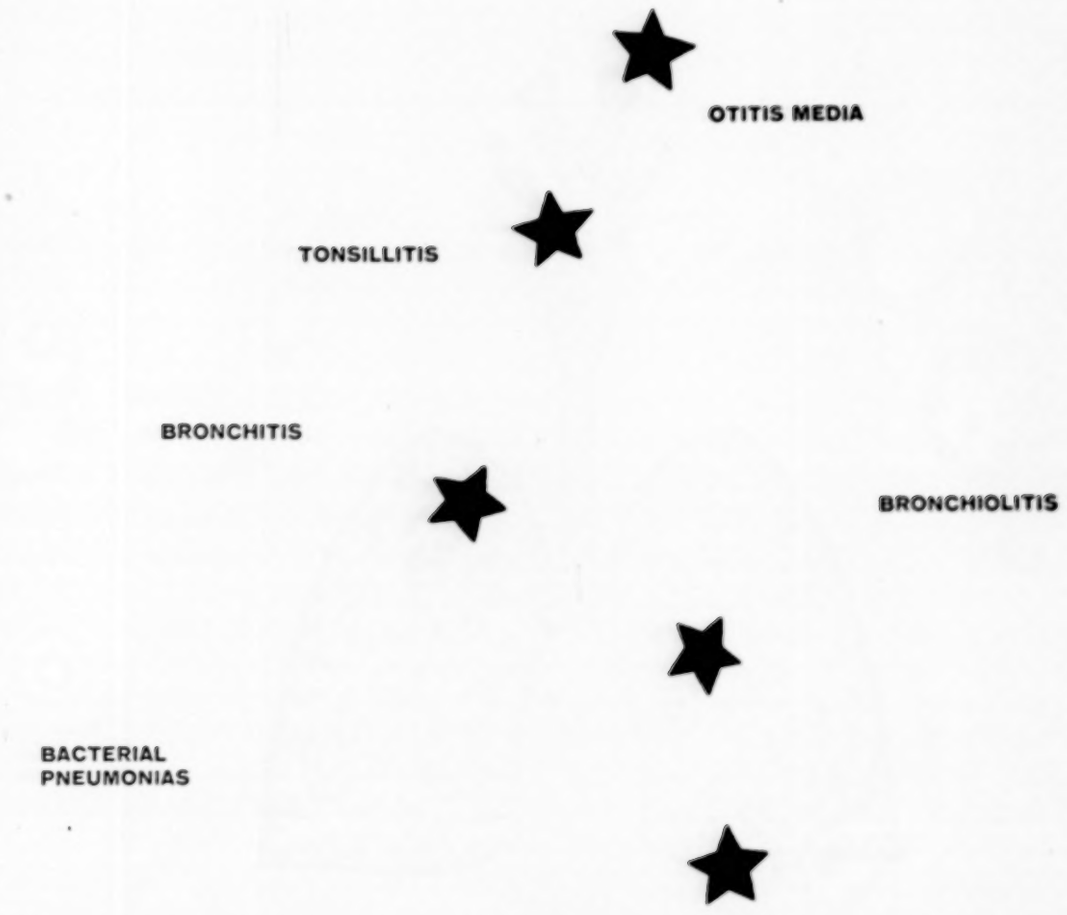

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An analysis of eighty-three cases of this cause of solitary indolent lymphadenitis, particularly of the axillary nodes, again emphasizes the prevalence of the infection—despite its relatively infrequent diagnosis—and brings out many interesting points about the disease. A skin reaction to the specific antigen remains the most useful confirmatory test, but about half of adults with the infection also give a positive lymphogranuloma venereum complement fixation test. The fever does not respond to antibiotics or other therapeutic measures but the course, fortunately, is self-limited.

Tuberculous Peritonitis. A Study of Forty-Seven Proved Cases Encountered by a General Medical Unit in Twenty-Five Years

W. R. BURACK AND ROBERT M. HOLLISTER 510

As indicated in this analysis of forty-seven cases, the diagnosis of tuberculous peritonitis remains elusive, particularly when it occurs with cirrhosis of the liver. No association of symptoms or signs is reliable, and laboratory confirmation fails in an appreciable proportion of cases. However, in a patient with ascites, with or without cirrhosis, who has unexplained abdominal pain or tenderness, or fever, the possibility of tuberculous peritonitis should be considered, even in the absence of demonstrable tuberculosis elsewhere. Suggestive findings in the ascitic fluid include a total protein content greater than 2.5 gm. per cent and more than 250 leukocytes per cu. mm. with a preponderance of lymphocytes.

An Experimental Malabsorption Syndrome Induced by Neomycin

EUGENE D. JACOBSON, ROBERT B. CHODOS AND WILLIAM W. FALOON 524

The familiar gastrointestinal effects of neomycin include a temporary state of malabsorption. The close resemblance of the broad spectrum of malabsorptive errors so produced to non-tropical sprue is brought out in this paper which describes reduced absorption from the gut of carotene, glucose, D-xylose, iron-59 and vitamin B_{12}, and a fall in serum cholesterol. By comparison with the effects of magnesium sulfate and castor oil it is made clear that the neomycin effects are not attributable simply to hypermotility of the bowel; nor, apparently, to changes in the bacterial flora of the intestines or poisoning of intestinal enzymes required for absorption. The authors favor the hypothesis that the drug induces inflammatory effects in the small intestinal mucosa which obstruct absorption.

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The Differential Effect of Drugs on the Proximal and Distal Colon
SIDNEY FINK AND GERALD FRIEDMAN 534

Registration of intraluminal pressures simultaneously in proximal and distal segments of the colon, before and after injection of appropriate drugs, gave additional evidence that the proximal (vagus innervated) and the distal (sacral innervated) halves of the colon are functionally distinct units. This concept deserves more attention in relation not only to the action of drugs but also in respect to the pathogenesis and course of colonic diseases.

Erythrocyte Dynamics in Liver Disease . . . . . CHARLES A. HALL 541

There is a good deal of uncertainty concerning the state of the red cell volume in patients with cirrhosis and other liver diseases, since measurements have ranged from low to normal to high, and also little clarification of the several factors which determine the red cell volume under these circumstances. The present study employs appropriate technics and calculations to measure the total red cell volume (found to be low in very few cirrhotic subjects), red cell life span (usually more or less reduced), the rate of red cell production (normal or increased). On the whole, then, this group of subjects with cirrhosis and other liver disorders managed to maintain normal or essentially normal erythrocyte dynamics.

A Rapid Screening Test for Deficiency of Plasma Ceruloplasmin and Its Value in the Diagnosis of Wilson's Disease
PHILIP AISEN, JULIAN B. SCHORR, ANATOL G. MORELL, RUTH Z. GOLD AND I. HERBERT SCHEINBERG 550

A simple spot test for ceruloplasmin is described, intended to screen children for latent Wilson's disease. There is a practical point involved, since early recognition and institution of preventive measures may obviate the clinical manifestations of hepatolenticular degeneration.

Studies on Copper Metabolism XXIX. A Critical Analysis of Serum Copper and Ceruloplasmin Concentrations in Normal Subjects, Patients with Wilson's Disease and Relatives of Patients with Wilson's Disease
G. E. CARTWRIGHT, H. MARKOWITZ, G. S. SHIELDS AND M. M. WINTROBE 555

Wilson's disease is associated with a disturbance in copper metabolism characterized by deficiency of ceruloplasmin, increased absorption of copper from the gastrointestinal tract, increased non-ceruloplasmin copper in the plasma, and excessive deposition of copper notably in certain tissues of predilection. Which, if any, of these abnormalities represents the primary genetically transmitted defect is still a matter of conjecture. The present study points up discrepancies between the ceruloplasmin concentration and the severity and duration of the clinical manifestations of Wilson's disease—a few patients with overt disease had ceruloplasmin levels within the lowest range of normal, and some symptom-free relatives had distinct ceruloplasmin deficiency. It is concluded that ceruloplasmin deficiency is not the primary metabolic defect in Wilson's disease.

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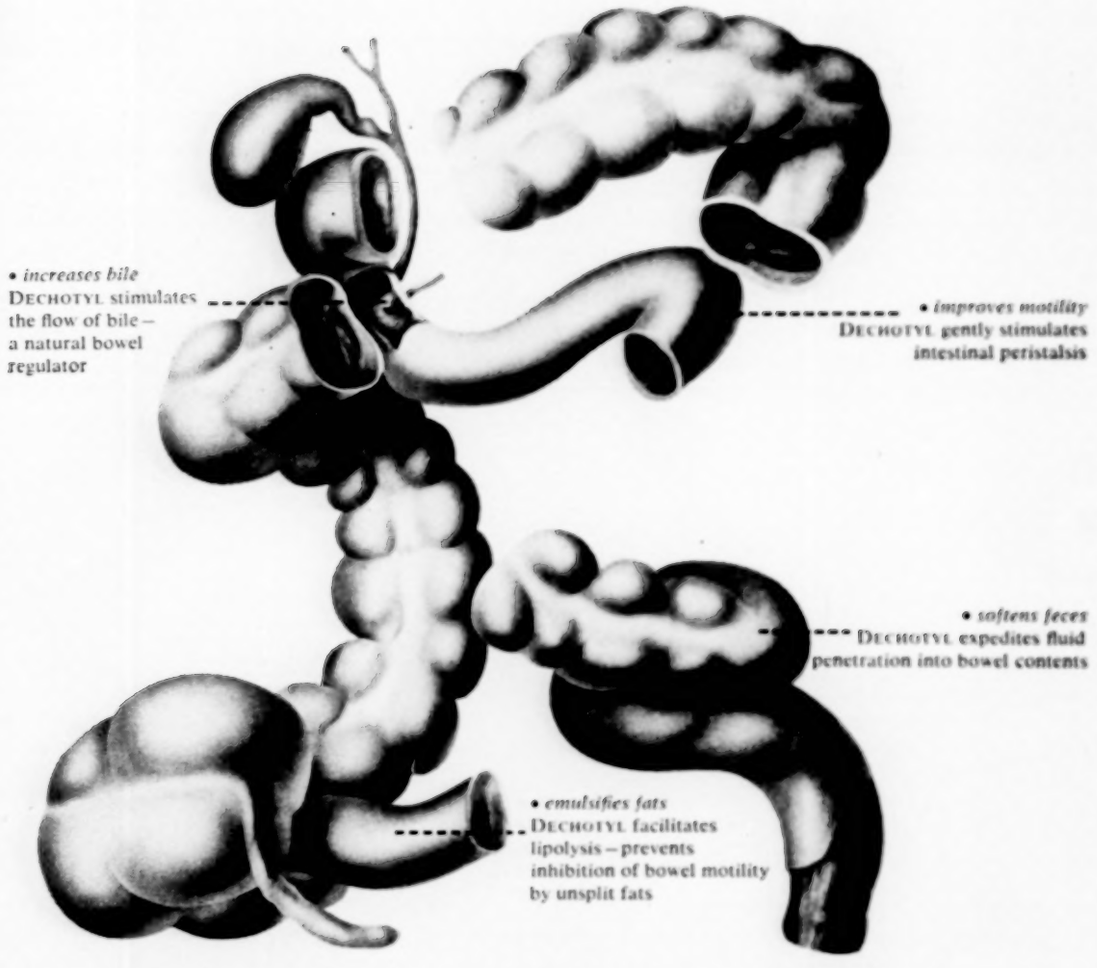
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Reviews

The Closing Mechanism at the Gastroesophageal Junction
GASTON VANTRAPPEN, E. CLINTON TEXTER, JR., CLIFFORD J. BARBORKA AND J. VANDENBROUCKE 564

While it is apparent that there must be some kind of closing mechanism at the gastroesophageal junction, elucidation of the nature and operation of this mechanism has proved to be extraordinarily difficult. The various proposals made in this connection are here set forth and discussed critically and in detail. It is indicated that a distinct anatomic sphincter, as such, does not exist, yet a physiologic sphincter is readily demonstrable by pressure measurements as a high pressure zone. The possible roles played by a flap-valve, the pinchcock action of the diaphragm and a rosette of mucosal folds are considered.

Gallop Rhythm of the Heart. I. Atrial Gallop, Ventricular Gallop and Systolic Sounds
JOSEPH GRAYZEL 578

An attempt is made in this careful study to correlate gallop rhythm with hemodynamic events of the heart. Gallop rhythm is a mechanical event associated with a relatively rapid rate of ventricular filling and characterized by a ventricular bulge and a low frequency sound. Systolic sounds therefore are not gallop sounds. Two types of gallop rhythm exist, *viz.*, "rapid filling" and "atrial" gallop, both diastolic in time. Cases are presented illustrating the mechanism involved, timing, and the clinical conditions producing these types of gallop rhythm.

Clinicopathologic Conference

Inferior Vena Caval Occlusion 593

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

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Hypophosphatasia in the Adult . . . . . J. E. Bethune and C. E. Dent 615

Hitherto described only in children, the authors record the presence of hypophosphatasia in two middle-aged sisters. Both show the characteristic low plasma alkaline phosphatase and urinary excretion of phosphoethanolamine, and interesting skeletal changes consistent with the disorder.

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An instructive case, well described.

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An interesting case instructively discussed.

Primary Hyperaldosteronism without Adrenal Tumor
Walter Moran, Frederick C. Goetz, James Melby, Bernard Zimmerman and B. J. Kennedy 638

Unequivocal evidence of primary hyperaldosteronism was obtained in an eighteen year old girl with marked hypertension. Surgical exploration, however, failed to reveal adrenal tumor or distinct hyperplasia; nevertheless subtotal adrenalectomy resulted in the return of the blood pressure to normal, and a correction of the metabolic abnormalities. The authors point to other such cases, all in subjects less than eighteen years of age at the time of diagnosis, and suggest that these cases represent a distinct form of congenital adrenal hyperfunction.

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Intrahepatic Cholestasis Following Administration of Chlorpropamide. Report of a Case with Electron Microscopic Observations
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This study adds yet another drug, a sulfonylurea compound, to the list of those causing intrahepatic cholestasis with jaundice.

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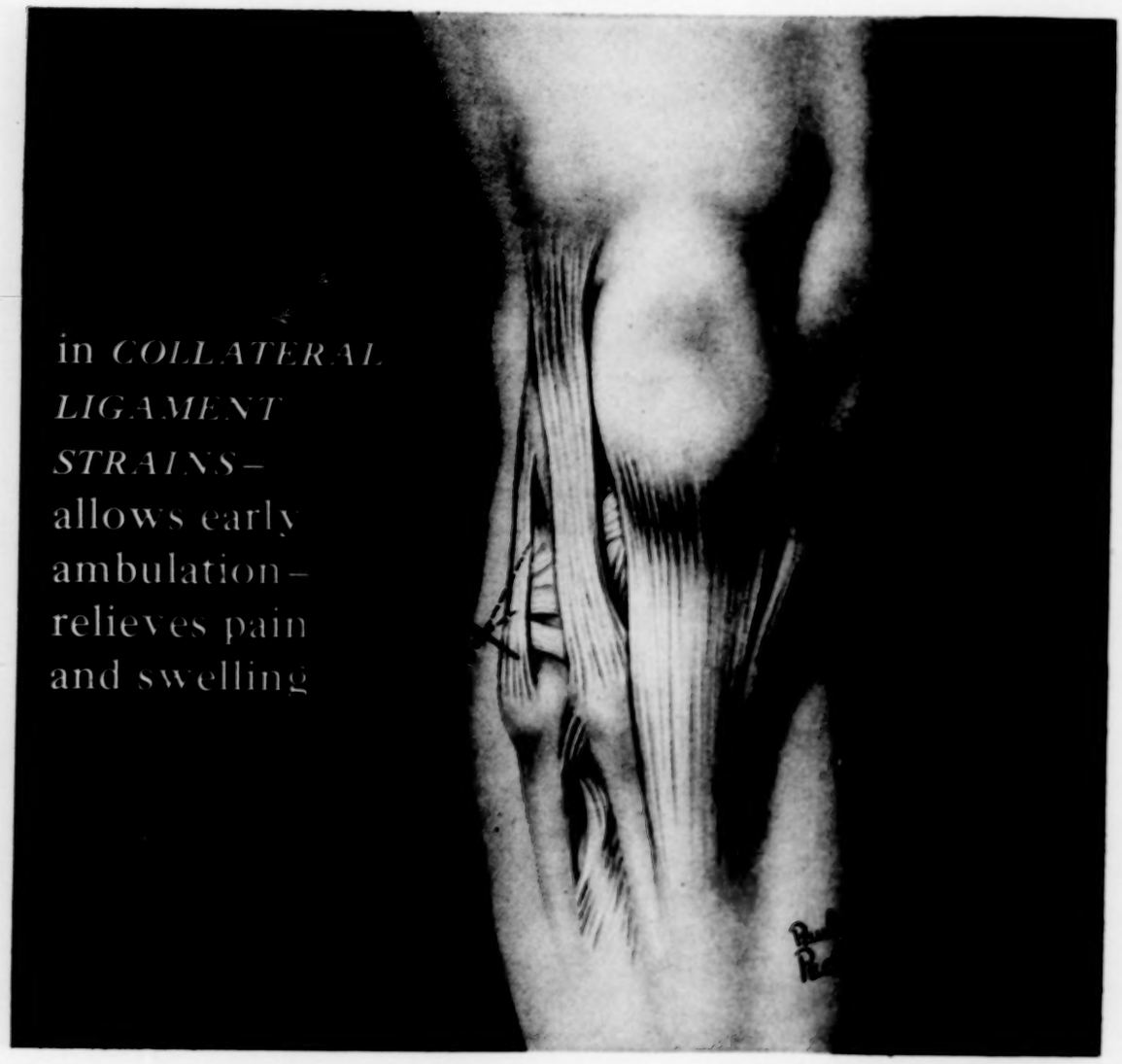

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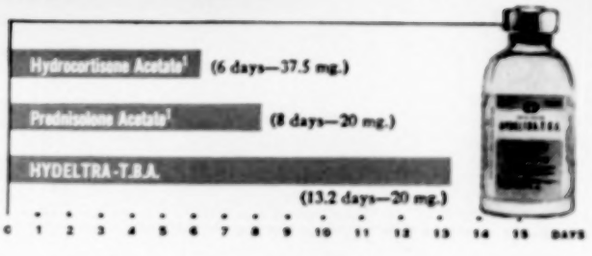
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EARL E. GAMBILL, WALTMAN WALTERS AND PAUL W. SCANLON 668

An instructive case.

PLEASE NOTE . . .

in the article "Liver Cell Necrosis in Chlorpromazine Jaundice (Allergic Cholangiolitis). A Serial Study of Twenty-Six Needle Biopsy Specimens in Nine Patients" which appeared on pages 708-729 of the November issue, all alkaline phosphatase values should be read as Shinowara-Jones-Reinhart units rather than Bodansky units as written.

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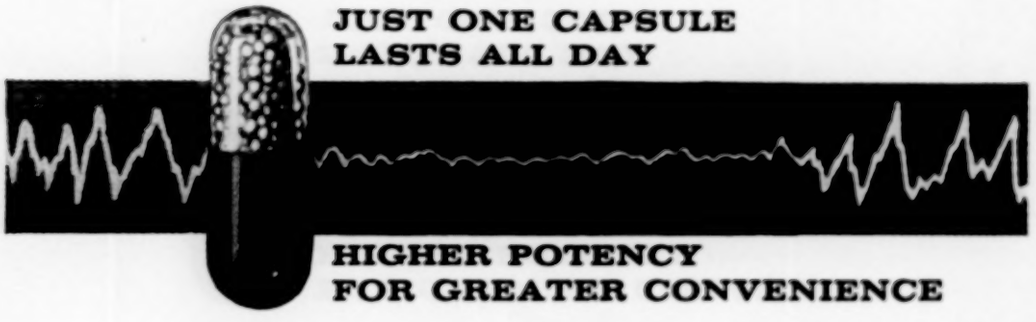

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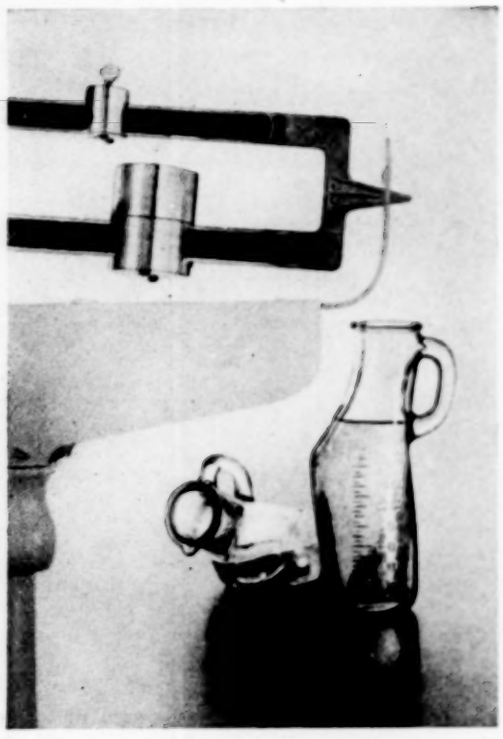

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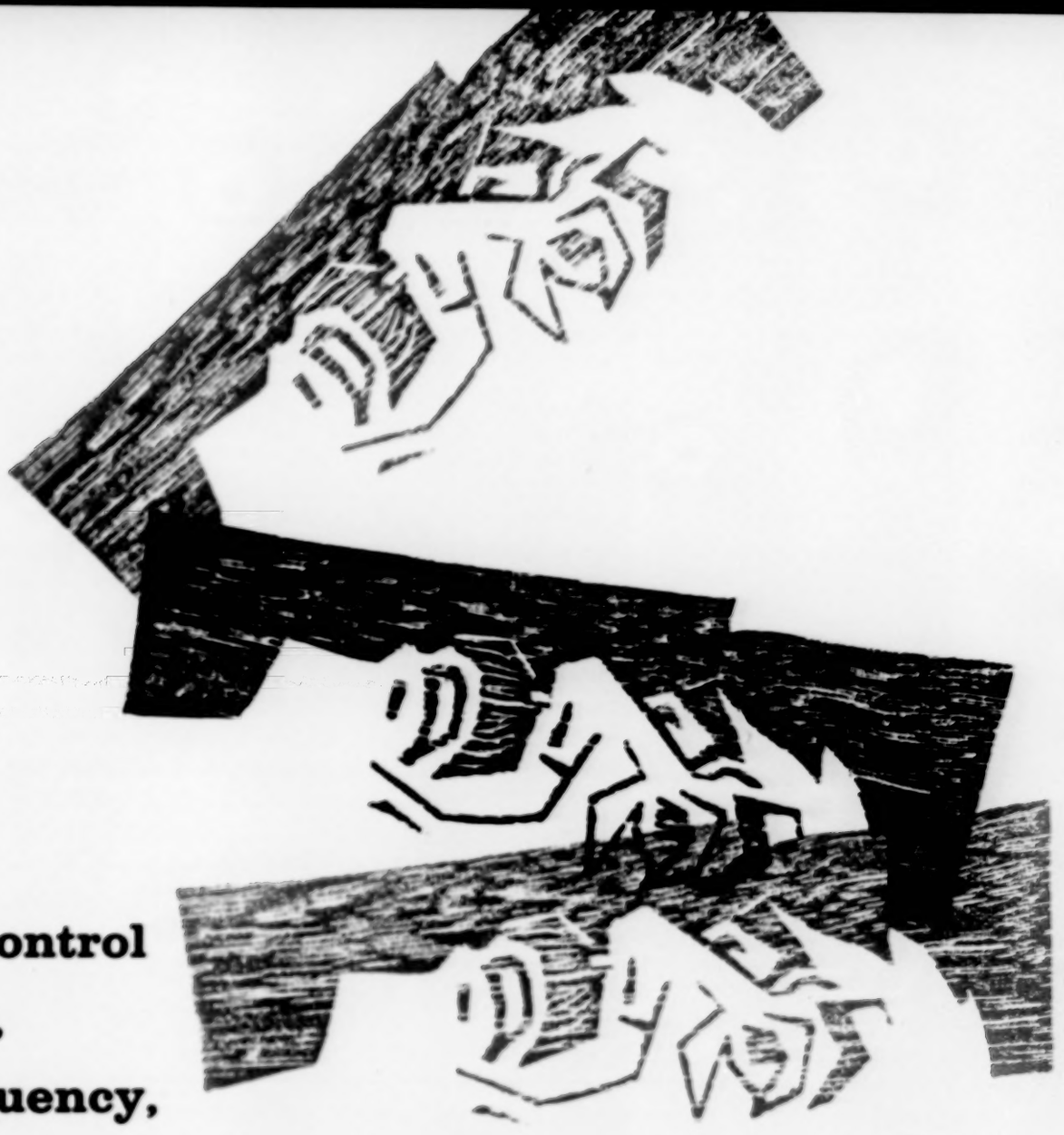

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2. Smith, Richard T.: New York Med. 8:16, 1952.

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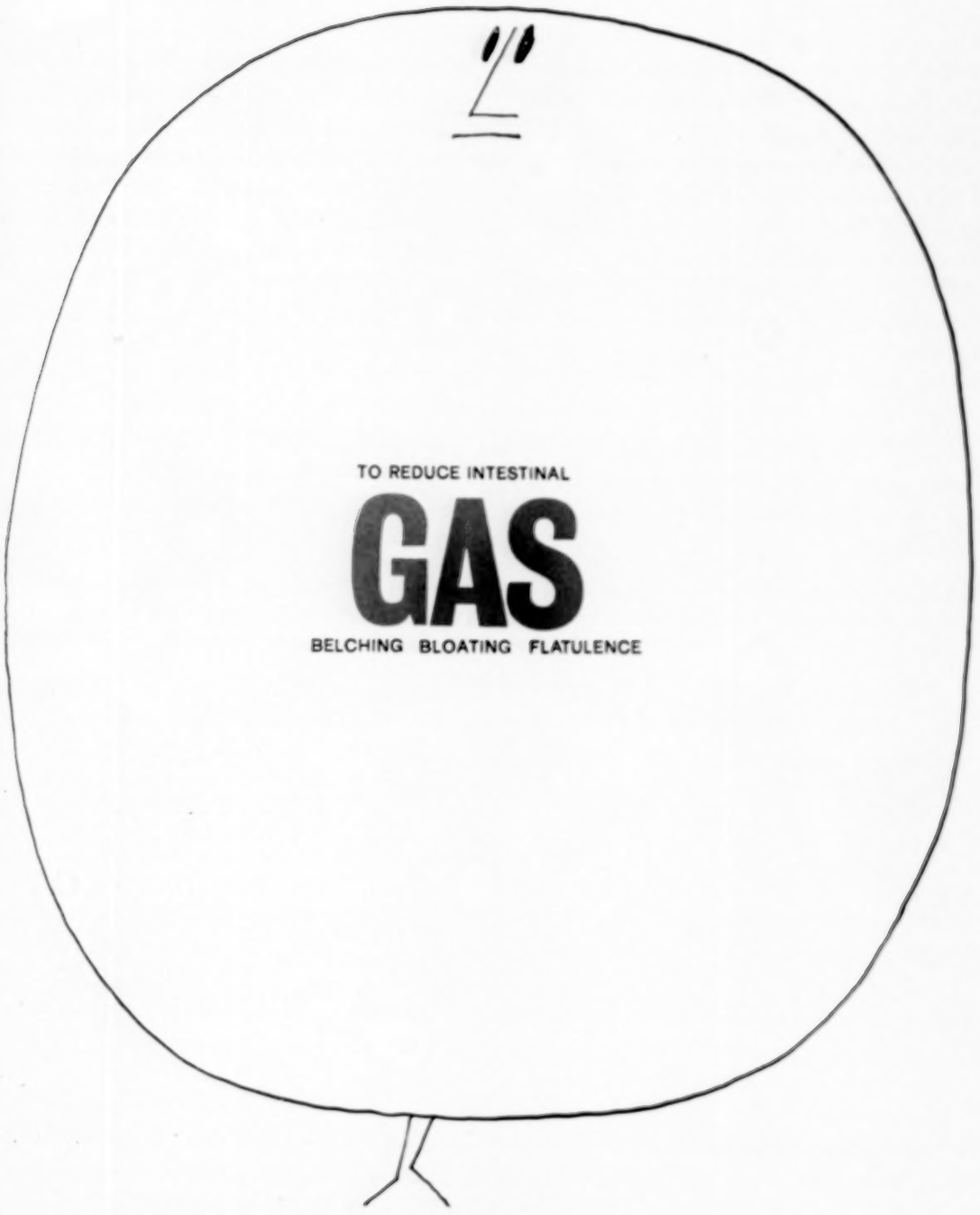
"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.

in renal edema

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

MSD MERCK SHARP & DOHME
Division of Merck & Co., Inc., Philadelphia 1, Pa.



TO REDUCE INTESTINAL

GAS

BELCHING BLOATING FLATULENCE

A biochemical compound used to diminish intestinal gas in healthy persons and those patients having digestive disorders ■

KANULASE

Each Kanulase tablet contains Dorase,* 320 units combined with pepsin, N.F., 150 mg.; glutamic acid HCl, 200 mg.; pancreatin, N.F., 500 mg.; oxbile extract, 100 mg. Dosage: 1 or 2 tablets at mealtime. Supplied: Bottles of 50 tablets.

*BRAND OF CELLULASE, EXPRESSED AS DIGESTIVE ACTIVITY UNITS

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Raudixin–the cornerstone of antihypertensive therapy–
helps relieve the pressures in your patients–helps
relieve the pressures on your patients / 50 and 100 mg. tablets
whole root rauwolfia for exceptional patient response

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Squibb Whole Root Rauwolfia Serpentina/'Raudixin'® is a SQUIBB TRADEMARK

for puzzling signs and symptoms...

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When signs and symptoms refuse to fall into place, the C.R.P.A. test accurately indicates inflammatory and necrotic diseases. A simple office procedure taking less than two minutes to set up and perform, the C.R.P.A. test can be used *prior to other tests* to determine the necessity for an erythrocyte sedimentation rate or SGO-T level.

Unlike the ESR or SGO-T level, a C.R.P.A. test demonstrates no variability in normal values. It is influenced only by the C-reactive protein in the patient's blood. A positive reaction always indicates pathology;[1] no false positives have ever been reported.

The C.R.P.A. test is a consistently constant indicator of acute myocardial infarction,[1-9] acute rheumatic fever,[10-12] active widespread malignant disease,[1,6,7,12,13] and bacterial infections.[1,5,7,14]

C·R·P·A® *test*

for routine blood chemistry

The reliability of the C.R.P.A. test makes it invaluable in differential diagnoses and routine work-ups. It may be used to deny or confirm ESR and SGO-T readings. Because it is so sensitive it can mark the progress of the disease and measure the effectiveness of therapy.[1,15]

References: 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 3. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:50, 1957. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 5. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 6. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 7. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompuu, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

Complete literature and bibliography available on request.

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how does **Mellaril** *differ from other potent tranquilizers?*

Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization, relieves anxiety, tension, nervousness,

but is virtually free of such toxic effects as

jaundice
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blood dyscrasia
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greater specificity of tranquilizing action results in fewer side effects

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such "diffuse" effects as anti-emetic action.

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specific, effective tranquilizer

"Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

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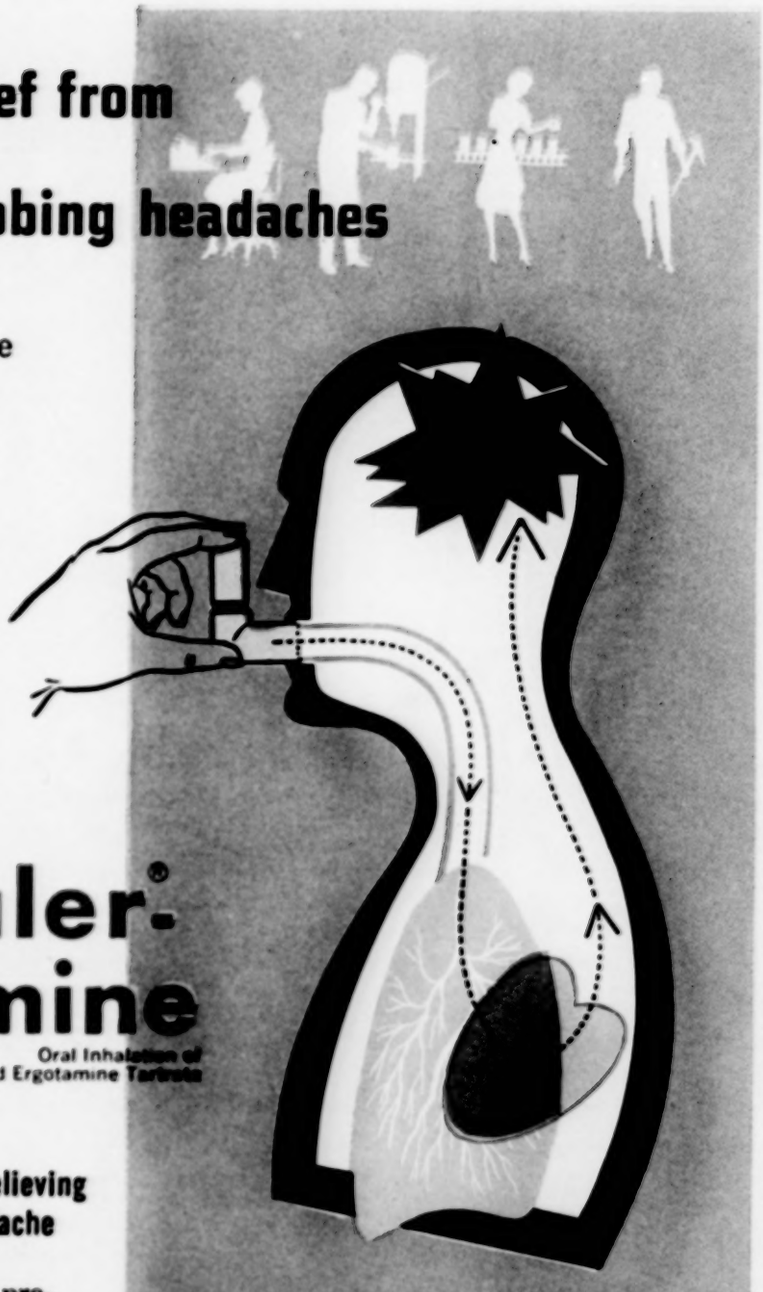
*Ostfeld, A. M.: Scientific Exhibit. American Academy of General Practice, San Francisco, April 6-9, 1959.

on-the-go relief from recurrent throbbing headaches

including migraine syndromes, other vascular headaches, histaminic cephalalgia, and occipital neuralgia



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Oral Inhalation of Micronized Ergotamine Tartrate

Fastest overall method for relieving recurrent throbbing headache

Approximates speed and predictability of relief following ergotamine injection.

Eliminates delay in treatment...Medihaler travels *with* the patient...ready and in use in 5 seconds!

"In a series of over 300 episodes of vascular headache in 41 patients 'Medihaler'-Ergotamine was effective in about 70%."

Graham, J.R.: Faulkner Hospital, Jamaica Plains, Boston.

Dosage: A single inhalation at onset of headache. Additional inhalations should be spaced not less than 5 minutes apart. Not more than 6 inhalations in any 24-hour period.

In 2.5 cc. stainless steel vial (80 doses) with plastic oral adapter. Each depression of metering valve delivers 0.36 mg. ergotamine tartrate self-propelled from the oral adapter.

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brand of meclizine hydrochloride ✡

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for morning sickness

DOSAGE:
One or two tablets give 24 hour protection. Administer at bedtime to prevent "next morning" sickness.

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basic by every standard

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"Also, there are fewer therapeutic failures when patients are treated with . . . [BONINE] than with the other drugs."[11]
"[BONINE] is highly effective in relieving the nausea and vomiting of pregnancy, providing also the advantage of prolonged action. Thus, patients need not anticipate medication in the early morning hours when nausea is at its worst."[12]

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". . . [BONINE] is a drug which is safe and nontoxic to both the mother and fetus and which is attended by a minimum of undesirable side effects."[3]

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"The incidence of side effects is very low and this agent exhibits less sedation and somnolence within therapeutic ranges than any of the effective antiemetic agents."[11]

"Side effects were conspicuous by their rarity."[12]

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convenience ✓

"The most striking advantage of . . . [BONINE] was that the administration of an effective dose only once daily, at bedtime, gave 24 hour protection, thus obviating the inconvenience and distress of repeating doses during the day."[4]
". . . [BONINE] is especially effective and has the advantages of a long duration of action (up to 24 hours) and a minimum of untoward side reactions."[1]

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A single low-dosage drug providing therapeutic benefit at reasonable cost . . . contains no unnecessary added ingredients that increase cost . . . requires no extended-action tablet structure for prolonged effect.

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experience ✓

The value of BONINE as an antinauseant has been well documented and is supported by six years of successful clinical use.[1-10]

only rarely does one drug meet so well the needs of one condition

REFERENCES: 1. Moyer, J. H.: M. Clin. North America, Mar., 1957, p. 405. 2. Lebherz, T. B., and Harris, J. H.: Obst. & Gynec. 6:606, 1955. 3. Mulherin, C. McL., and Bryans, C. I., Jr.: J. M. A. Georgia 45:146, 1956. 4. Bass, W. F.: Mississippi Doctor 32:176, 1954. 5. Seidner, H. M.: Illinois M. J. 109:20, 1956. 6. Charles, C. M.: Geriatrics 11:110, 1956. 7. Weil, L. L.: J. Florida Acad. Gen. Practice 4:9, No. 3, 1954. 8. Kinney, J. J.: J. M. Soc. New Jersey 53:128, 1956. 9. Semmens, J. P.: Obst. & Gynec. 9:586, 1957. 10. Conner, P. K., Jr., and Moyer, J. H.: GP 14:124, No. 5, 1956. 11. Daeschner, C. W., et al.: South. M. J. 49:1465, 1956. 12. Report of study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755, 1956. 13. Kean, B. H.: GP 20:112, No. 6, 1959. 14. Seppanen, A.: Geriatrics 14:457, 1959. 15. Harriman, E. F.: North Carolina M. J. 20:298, 1959. 16. Master, A. M.: New York J. Med. 58:2712, 1958.

SUPPLIED
BONINE Tablets, scored, 25 mg.
BONINE Chewing Tablets, mint-flavored, 25 mg.
BONINE Elixir, cherry-flavored, equiv. 12.5 mg./5 cc.

Professional Information Available on Request

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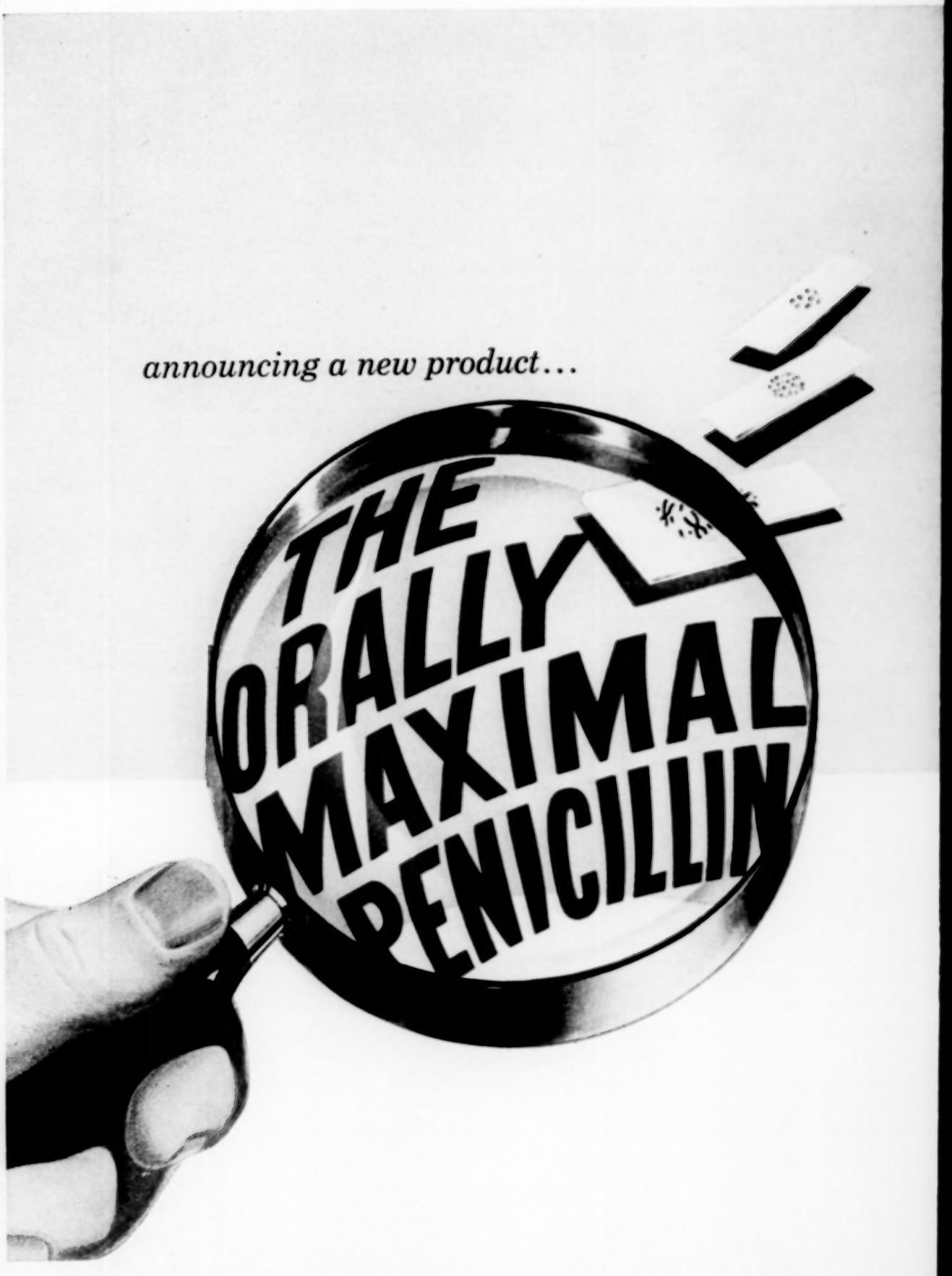
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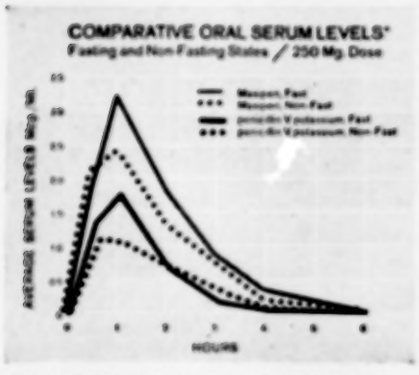

*Based on 3294 individual serum antibiotic determinations. Complete details on request.

MAXIMAL FLEXIBILITY May be administered without regard to meals. However, highest absorption is achieved when taken just before or between meals.

MAXIMAL ORAL INDICATIONS Indicated in infections caused by streptococci, pneumococci, susceptible staphylococci, and gonococci, including:

pneumococcal pneumonia	impetigo
gonorrhea	susceptible staphylococcal abscesses (with indicated surgery)
tonsillitis	cellulitis
laryngitis	lymphangitis
otitis media	pyoderma
streptococcal pharyngitis	

Also prophylactically in secondary infections following tonsillectomy, dental extractions, other surgical procedures.

Dosage: For moderately severe conditions, 125 to 250 mg. three times daily. For more severe conditions, 500 mg. as often as every four hours around the clock.

Note: To date, MAXIPEN has not shown less allergic reactions than older oral penicillins. Usual precautions regarding administration should be observed.

Supplied: MAXIPEN TABLETS, scored, 125 mg. (200,000 units) bottles of 36; 250 mg. (400,000 units) bottles of 24 and 100.
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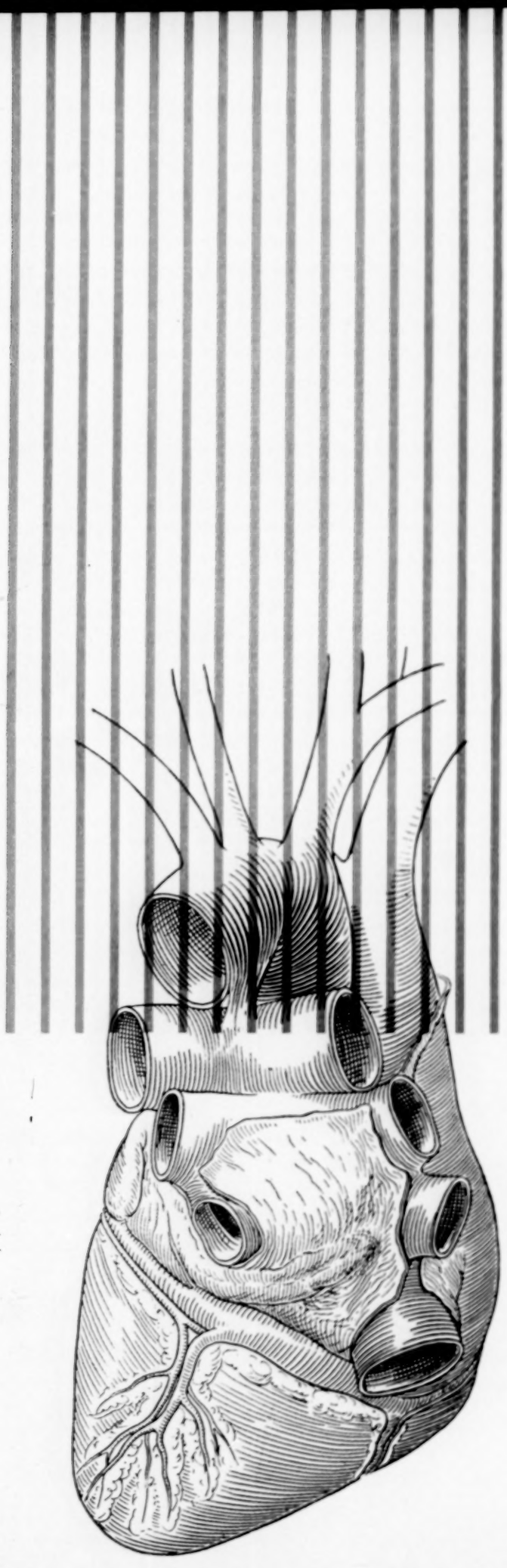

Now, a single agent, important clinical

for total management of angina pectoris

Marplan prevents pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.[1-6] To date, Marplan prophylaxis has been evaluated in over 300 angina patients. The response rate was 76 per cent with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1] One study reported "excellent effects with relatively small doses" and "greater relief than [with] any other compound in our experience."[2]

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris and, while it frequently abolishes anginal pain, Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.

with two distinct primary effects, for two indications

Marplan

a happy balance of potency/safety

A broad clinical research program continues to define the full range of Marplan's clinical applicability. However, already some 300 research clinicians have evaluated Marplan in more than 4000 patients in two primary diagnostic categories—*angina pectoris and depression.*

Marplan has been shown to be considerably more active than other amine oxidase regulators. While clinically such increase in potency has heretofore been associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of the side reactions of the hydrazines. Moreover, throughout the extensive clinical investigations, no liver damage has been reported. Marplan is an amine oxidase regulator, however, and like all of these agents, it is contraindicated in the presence of liver or kidney disease.

Consult complete literature and dosage instructions, available on request, before prescribing.

Bibliography: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Ohlath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. I. Kimbell, paper read at Cooperative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959.

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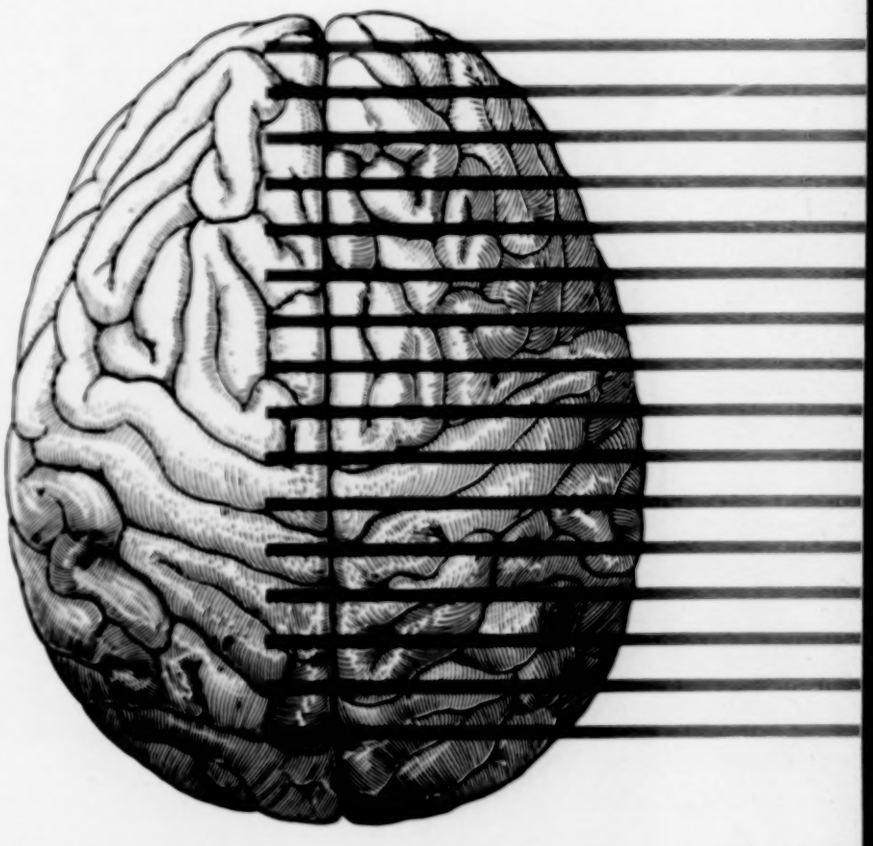
to lift depression

The value of Marplan in depression: Marplan is indicated in the broad range of emotional and psychiatric disorders with associated symptoms of depression, withdrawal or regression. To date, Marplan has been fully evaluated in more than 3700 patients with depression. The majority (67 per cent) showed significant improvement[1]: "Depression of mood and somatic preoccupation were less pronounced, concentration improved, irritability lessened, and the patients appeared to be more relaxed."[4]

Marplan in rheumatoid arthritis: Marplan has also been found to be valuable adjunctive therapy in the management of rheumatoid arthritis and other chronic debilitating disorders with associated depressed psychomotor activity.



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PATHIBAMATE combines two highly effective and well-tolerated therapeutic agents:

meprobamate (400 mg. or 200 mg.) widely accepted tranquilizer and . . .

PATHILON (25 mg.)—anticholinergic noted for its peripheral, atropine-like action, with few side effects.

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Two dosage strengths—PATHIBAMATE-400 and PATHIBAMATE-200 facilitate individualization of treatment in respect to both the degree of tension and associated G. I. sequelae, as well as the response of different patients to the component drugs.

Supplied: **PATHIBAMATE-400**—Each tablet (yellow, ½-scored) contains meprobamate, 400 mg.; PATHILON tridihexethyl chloride, 25 mg.
PATHIBAMATE-200—Each tablet (yellow, coated) contains meprobamate, 200 mg.; PATHILON tridihexethyl chloride, 25 mg.

Administration and Dosage: **PATHIBAMATE-400**—1 tablet three times a day at mealtime and 2 tablets at bedtime.
PATHIBAMATE-200—1 or 2 tablets three times a day at mealtime and 2 tablets at bedtime.
Adjust to patient response.

Contraindications: glaucoma; pyloric obstruction, and obstruction of the urinary bladder neck.

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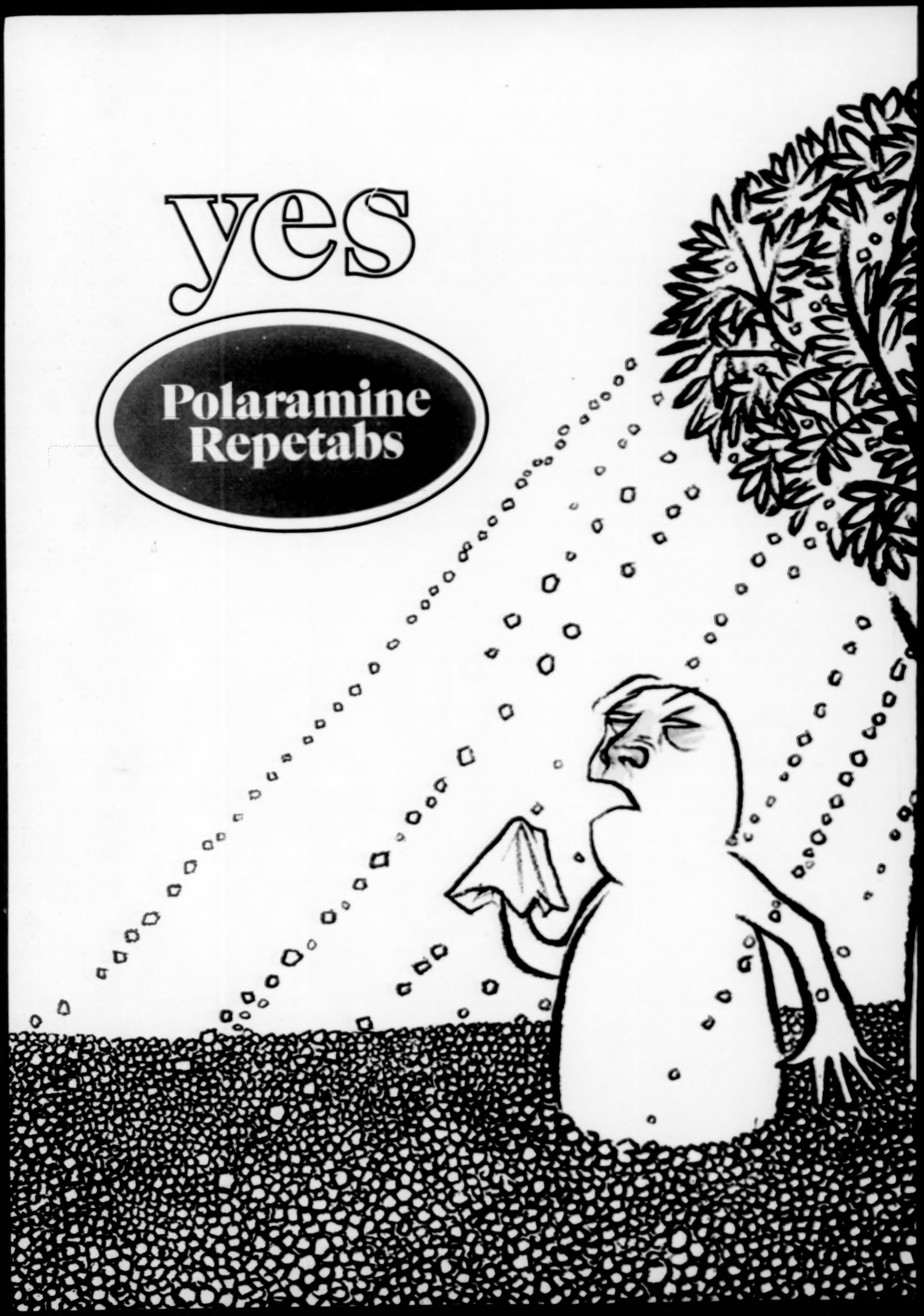
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answer the question of how to treat the patient allergic to tree pollens. (Birch, hickory and oak are the most important offenders, and oak is the most abundant.) With POLARAMINE REPETABS — today's lowest-dosage *anti*histamine — you can control rapidly and safely the annoyance and discomfort of seasonal or nonseasonal allergies, allergic dermatoses, allergic complications of respiratory illnesses, and drug and serum reactions.

Histamine is present in most tissues of the body, but it is concentrated in those body areas exposed to contact with the external environment: the skin, the respiratory tree, and the upper gastrointestinal tract. When an antigen, whether from tree pollen or any other allergenic substance, provokes an antibody response, histamine is released, and the familiar symptoms of allergy follow. POLARAMINE — in *any* form — controls these allergic reactions by blocking the access of histamine to receptor sites, and POLARAMINE does this at dosages lower than those necessary with other available antihistamines.

POLARAMINE REPETABS (4 mg. and 6 mg. dosage forms for your patients' convenience) and POLARAMINE Tablets (2 mg.) are unrivaled in effectiveness and safety. The rapidity of action for which POLARAMINE is noted is also important to the physician. Summarizing treatment of a recent group of 100 allergic patients, Babcock and Packard report that POLARAMINE REPETABS were "... especially effective in patients who presented sudden, acute allergy symptoms."*

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Dosage: **REPETABS, 6 mg. and 4 mg. — One REPETAB in the morning and one REPETAB in the evening. Tablets, 2 mg. — One t.i.d. or q.i.d.; children under 12, one-half tablet t.i.d. or q.i.d.; infants, one-quarter tablet t.i.d. or q.i.d. Syrup, 2 mg. per 5 cc. — Adults, one teaspoonful t.i.d. or q.i.d.; children under 12, one-half teaspoonful t.i.d. or q.i.d.; infants, one-quarter teaspoonful t.i.d. or q.i.d.**

Supply: **POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000; 4 mg., bottles of 100 and 1000. Tablets, 2 mg., bottles of 100 and 1000. Syrup, 2 mg. per 5 cc., 16 oz. bottles.**

****Babcock, G., Jr., and Packard, L. A.: Clin. Med. 6:985 (June) 1959.***

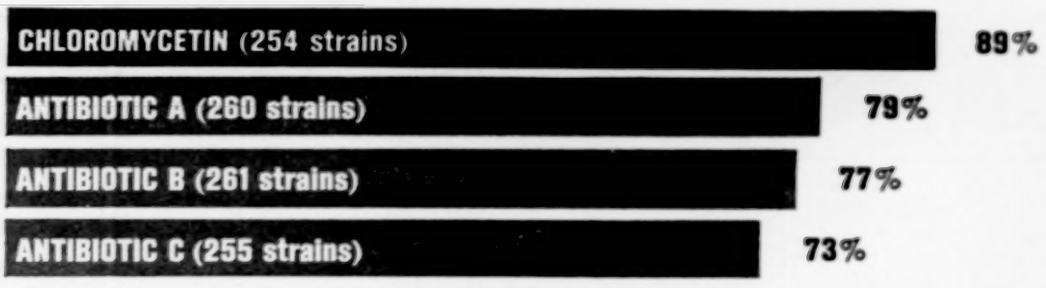
POLARAMINE® Maleate, brand of dexchlorpheniramine maleate. REPETABS,® Repeat Action Tablets. EN-1499

True broad-spectrum coverage... proved clinical efficacy

CHLOROMYCETIN®

OUTSTANDINGLY EFFECTIVE AGAINST A WIDE RANGE OF PATHOGENS

IN VITRO SENSITIVITY OF GRAM-POSITIVE ORGANISMS TO CHLOROMYCETIN AND TO THREE OTHER BROAD-SPECTRUM ANTIBIOTICS*



IN VITRO SENSITIVITY OF GRAM-NEGATIVE ORGANISMS TO CHLOROMYCETIN AND TO THREE OTHER BROAD-SPECTRUM ANTIBIOTICS*

*Adapted from Leming, B. H., Jr., & Flanigan, C., Jr., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 414.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy. 83760

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Tension Headache

Relief without Analgesics

"Meprobamate was found of considerable value in reducing the tension component of chronic headache, and thus decreasing the frequency and severity of attacks. No intolerance, dependence, or side effects were noted. . . ."
Blumenthal, L.S., and Fuchs, M.: Am. Pract. & Digest Treat. 9:1121 (July) 1958.

An extensive bibliography attests to the striking effectiveness and noteworthy safety of EQUANIL (meprobamate, Wyeth) in a variety of tension and anxiety states. EQUANIL possesses specific action; pharmacological action is not diffuse. Rapid metabolism precludes cumulative effects.

Although rare, allergic reactions may occur; excessive dosage should be avoided in all patients. For further information on prescribing and administering EQUANIL see descriptive literature, available on request.

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Meprobamate, Wyeth

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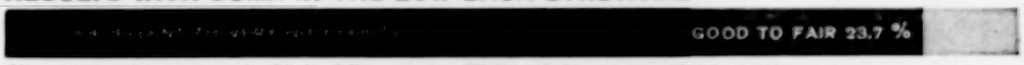
A Century of Service to Medicine

in the low back syndrome

relieves both stiffness and pain with safety... sustained effect

In 100 consecutive patients with the low back syndrome, Kestler[1] reported that particularly gratifying was the ability of SOMA "to relax muscular spasm, relieve pain, and restore normal movement, thus speeding recovery in a large majority of the patients."

RESULTS WITH SOMA IN THE LOW BACK SYNDROME*



*Investigators' reports to the Medical Department, Wallace Laboratories. (Total of 278 cases)

NOTABLE SAFETY—extremely low toxicity; no known contraindications; side effects are rare; drowsiness may occur, usually at higher dosage

RAPID ACTION—starts to act quickly **SUSTAINED EFFECT**—relief lasts up to 6 hours

EASY TO USE—usual adult dosage is one 350 mg. tablet 3 times daily and at bedtime

SUPPLIED—as white, coated 350 mg. tablets, bottles of 50; also available for pediatric use: 250 mg., orange capsules, bottles of 50

SOMA T. M.

(carisoprodol Wallace)

1. Kestler, O.: In The Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State University Press, Detroit, 1959. 2. Berger, F. M.; Kletzkin, M.; Ludwig, B. J.; Margolin, S., and Powell, L. S.: J. Pharm. Exp. Ther. *127*:66 (Sept.) 1959. 3. Spears, C. E. and Phelps, W. M.: Arch. Pediat. 76:287 (July) 1959. 4. Phelps, W. M.: Arch. Pediat. 76:243 (June) 1959. 5. Friedman, A. P.; Frankel, K., and Fransway, R. L.: Papers presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc. ,New York, Sept. 30, 1959. 6. Kuge, T.: Unpublished reports. 7. Ostrowski, J. P.: Orthopedics (In Press).

Literature and samples on request

Also available on request: The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959. (185 pages)

WALLACE LABORATORIES, New Brunswick, New Jersey

90% of anxious, agitated and apathetic office patients calmed without drowsiness and with normal drive restored...

on one or two 0.25 mg. tablets b.i.d.:

This is the pattern of performance for

PERMITIL®

Fluphenazine dihydrochloride

In Anxiety and Anxiety-induced Depression

"In contrast to other phenothiazines, it [PERMITIL] mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."[1]

- In 608 patients with anxiety and anxiety-induced fatigue or depression, PERMITIL, administered in small daily doses of 0.5 mg. to 1 mg., produced significant improvement in 90%.[2]
- PERMITIL is virtually free from side effects at recommended dosage levels.
- Patients become calm without being drowsy and normal drive is restored.
- Onset of action is rapid; effect is prolonged.
- PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

How to prescribe PERMITIL: The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

SUPPLIED: Tablets, 0.25 mg., bottles of 50 and 500.

REFERENCES: 1. Ayd, F. J., Jr.: Current Therapeutic Research 1:41 (Oct.) 1959. 2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.

PERMITIL

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

new
for angina pectoris:

Often Succeeds in Difficult Cases

Among 48 patients[4] previously treated with other coronary vasodilators, ISORDIL was demonstrably superior in 37, equivalent in 9, inferior in 2.

Markedly Reduces Attacks

Albert[3] found that 92 per cent of patients responded favorably to ISORDIL. During this study, anginal attacks were reduced from an average of 5 a day to just 1.2 a day.

Benefits Confirmed by EKG's

Electrocardiographic studies by Russek[2] clearly show that ISORDIL produces a more favorable balance between oxygen supply and demand following the Master two-step test.

"The most effective medication for the treatment of coronary insufficiency available today."

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prompt, prolonged coronary vasodilatation

1 rapid onset ISORDIL acts rapidly compared with other prophylactic agents—patients usually experience benefits within 15 to 30 minutes. Virtually eliminates unprotected periods.

2 prolonged action The beneficial effects of a single dose persist for at least 4 hours—therefore for most patients q.i.d. dosage is highly satisfactory.

3 consistent effect Response of patients treated in various clinical studies[1] to date was 85 per cent good, 7 per cent fair, and 8 per cent unsatisfactory.

4 unusual safety The only side effect reported has been transitory, easily controlled headache, normally considered an expression of effective pharmacodynamic activity.[2]

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"ISORDIL is a new and effective agent for therapy of angina pectoris."
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In addition to the effectiveness required in challenging conditions, Tigan provides the safety which assumes special significance in everyday situations. Tigan shares the superior antiemetic potency (and mechanisms of action[5]) of the phenothiazines without entailing any of their risks or, for that matter, any of the side effects

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safely controls the entire range of emetic situations without antihistamine side effects and without phenothiazine risks

of the antihistamines.[6-9] No sedation or other side effects were observed in TRAVEL SICKNESS patients, who were quickly and efficiently relieved by Tigan.[10] Nor was any drowsiness or other untoward reaction seen in 16 PREGNANT women, 15 of whom became asymptomatic on Tigan, while other antiemetic medication had failed or caused drowsiness in several.[10] In GASTROINTESTINAL vomiting, where results were "good" in 86 per cent and "fair" in 14 per cent, Tigan was "well tolerated" by all.[11]

TIGAN (COMPARED TO PLACEBO) IN SEASICKNESS

Medication	Number of Patients	RESULTS	
		Improved	Unimproved
Tigan, given initially	142	133	9
Placebo, given initially	74	7	67
Tigan, given after failure of placebo	65	61	4

NO SPECIAL PRECAUTIONS OR CONTRAINDICATIONS—Patients on Tigan may drive an automobile or operate other mechanical equipment without the hazard of drowsiness; and carry on household activities without lethargy or sleepiness.

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With its wide spectrum, Gantrisin covers all pathogens predominant in the urinary tract,[1,3-5] including many resistant strains. Its use in cystitis[2-5,6] often achieves better control than "...some of the more expensive antibiotics."[1]

ASSURES SAFETY THROUGH HIGH SOLUBILITY

The low toxicity and high solubility of Gantrisin[1-3,5] are especially important when dysuria in cystitis contraindicates fluid-forcing[1] or when prolonged therapy is required.[3]

PROVIDES ROUTINE PROPHYLAXIS

In routine prophylaxis[7,8] after surgery and manipulations, Gantrisin significantly reduces the incidence and severity of cystitis. Results here have been termed "excellent."[8]

References

1. O. S. Lowsley and T. J. Kirwin, *Clinical Urology*, ed. 3, Baltimore, The Williams & Wilkins Co., 1956, vol. 2, pp. 490 ff., 975. 2. J. J. Robbins, *J. Kentucky M.A.*, *56*:47, 1958. 3. E. J. Richardson in H. F. Conn, Ed., *Current Therapy 1957*, Philadelphia, W. B. Saunders Co., 1957, pp. 330 ff. 4. W. J. Reich and M. J. Nechtow, *Practical Gynecology*, ed. 2, Philadelphia, J. B. Lippincott Co., 1957, pp. 337-338. 5. J. T. Mason in H. E. Conn, Ed., *Current Therapy 1959*, Philadelphia, W. B. Saunders Co., 1959, p. 342. 6. J. R. Hand in H. E. Conn, Ed., *Current Therapy 1959*, Philadelphia, W. B. Saunders Co., 1959, p. 409. 7. E. M. Yow, *Am. Pract. & Digest Treat.*, *4*:521, 1953. 8. W. E. Studdiford, Jr., *S. Clin. North America*, *34*:293, 1954.

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SYMPOSIUM REPORT:

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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

*Experimental dosage (see dosage recommendations adjacent)

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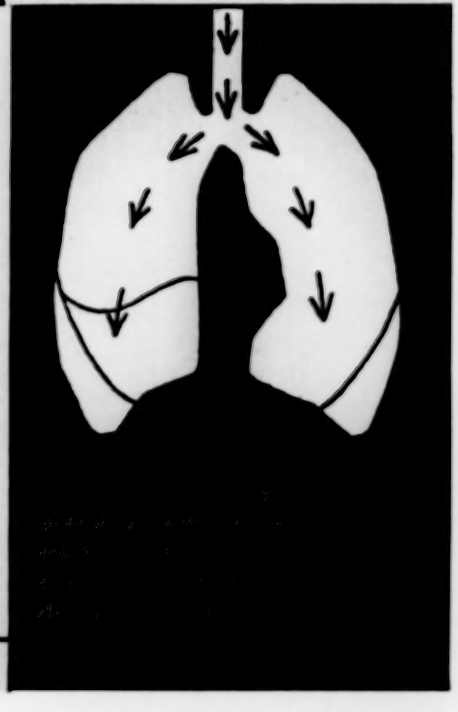

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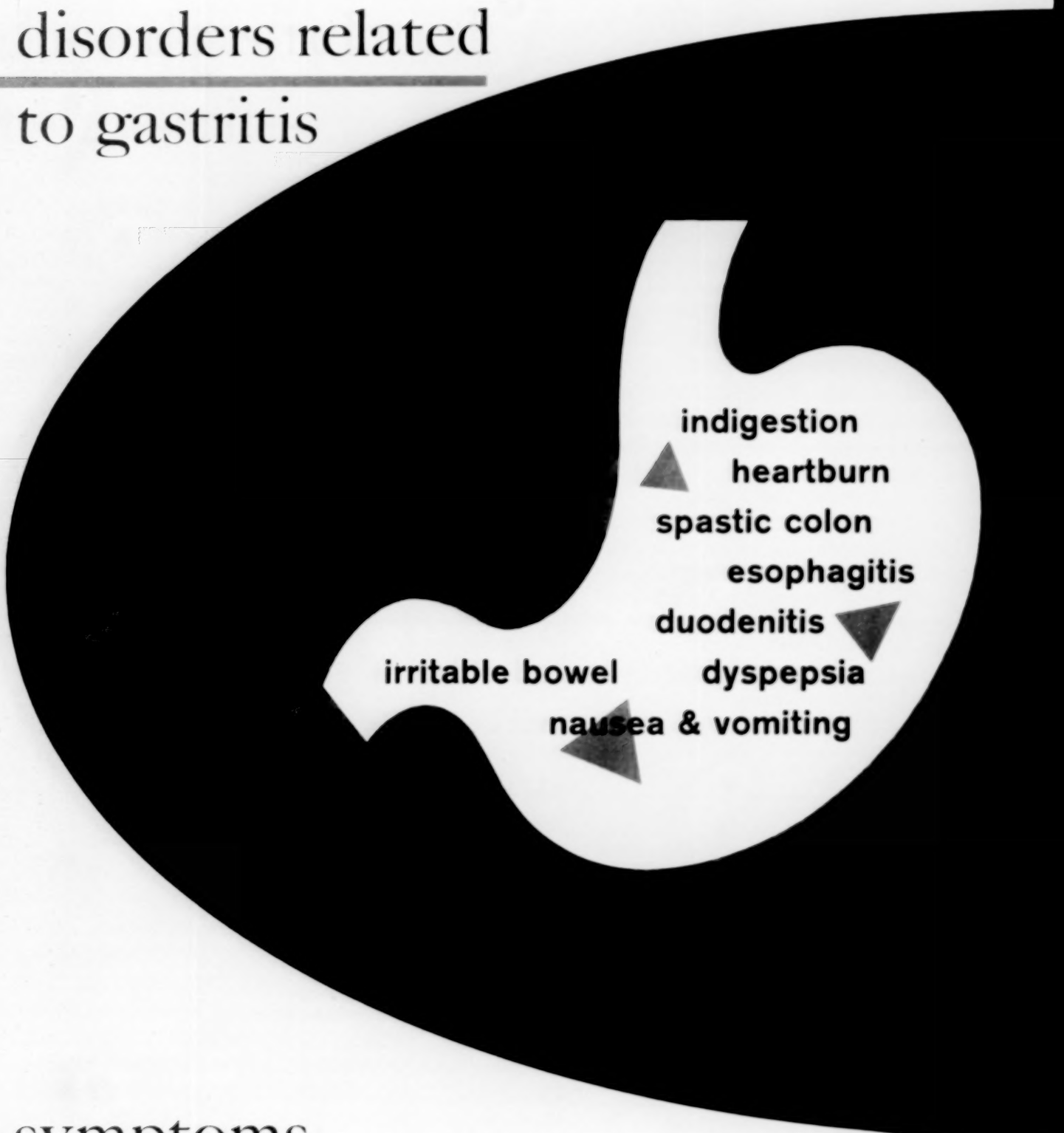

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Deutsch, E., and Christian, H.J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

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References:
1. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. *1*:552, 1958. 2. Gutman, A. B., and Yü, T. F.: Bull. N. Y. Acad. Med. *34*:287, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. *17*:326, 1958. 4. Ogryzlo, M. A., and Harrison, J.: Ann. Rheumat. Dis. *16*:423, 1957.

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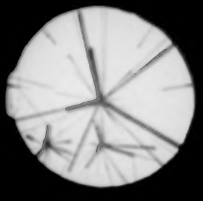

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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

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2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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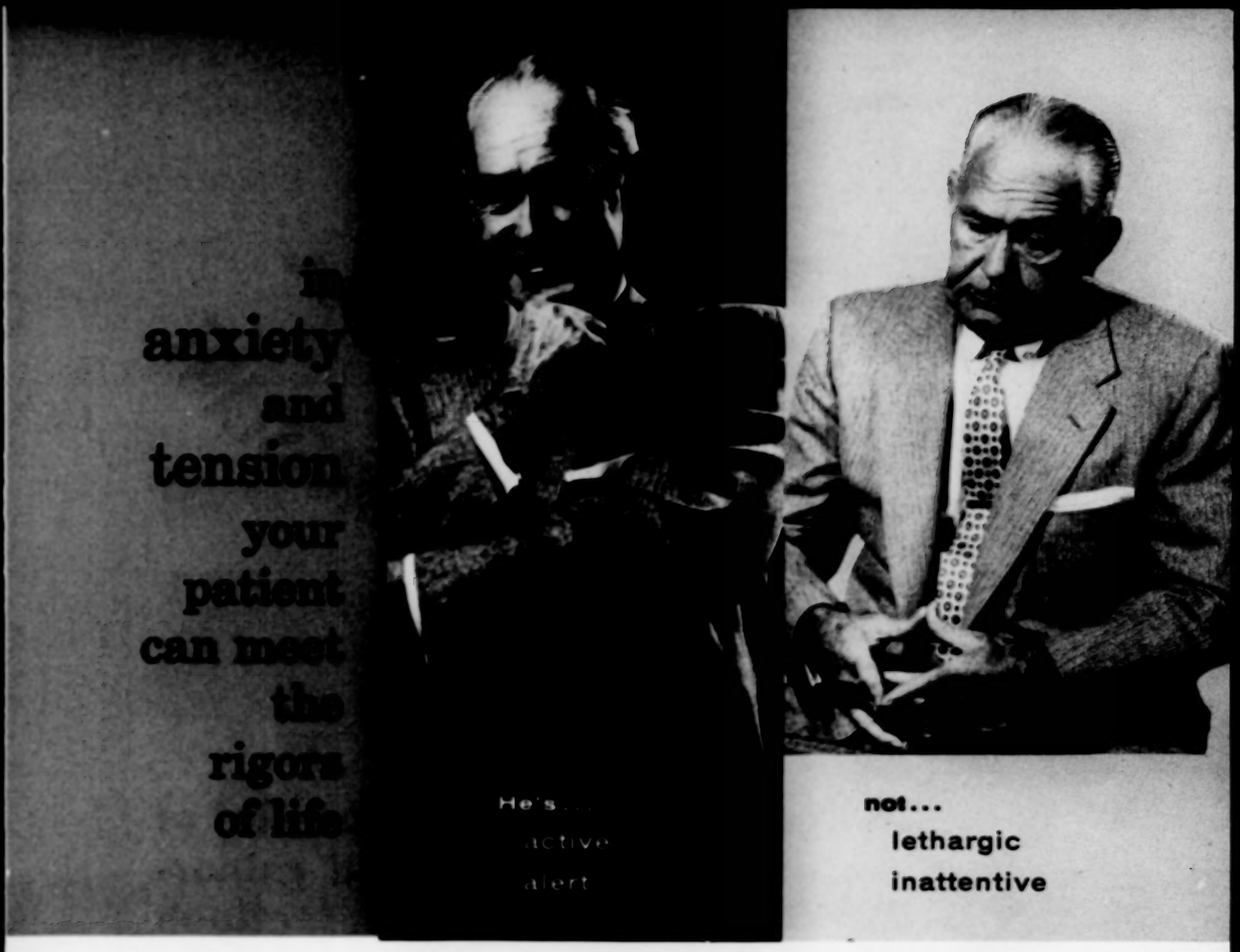

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1. Batterman, R. C.; Grossman, A. J.; Mouratoff, G. J., and Leifer, P.: A Clinical Re-evaluation of Daytime Sedatives, Scientific Exhibit, Annual Meeting of AMA, San Francisco, June 23-27, 1958.
2. Grossman, A. J.; Batterman, R. C., and Leifer, P.: Fed. Proc. *17*:373 (March) 1958.

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